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HYDROLYSED CASEIN FOR PARENTERAL ADMINISTRATION TO INFANTS

BY

YVONNE J. WILLIAMS, M.D., E. A. BISHOP, M.B., B.S., D.C.H., and W. F. YOUNG, M.D., D.C.H.

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Since the year 1939, when preparations of protein digests became generally available in America, reports of investigations designed to test their value in the parenteral feeding of infants have appeared from time to time. 'Amigen,' an enzymic digest of hydrolysed casein, is one of these preparations. Shohl, Butler, Blackfan, and McLachlan (1939), using 'amigen' as the sole source of nitrogen in the diets of normal infants, found that it was as well utilized as the nitrogen supplied by an evaporated milk mixture so composed as to supply a similar quantity of food with the same percentage composition. Moreover, it was found that if the 'amigen' (again as the sole source of nitrogen) were given intravenously for periods of twenty-four hours, the subjects were still kept in a positive nitrogen balance comparable in magnitude with the balance obtained when the 'amigen' was given by mouth. Shohl (1943) also was able to show that infants suffering from gastro-enteritis were maintained in positive nitrogen balance when 'amigen' was given intravenously in quantities sufficient to provide the protein equivalent of at least 2·2g. per kg. per day, whereas similar infants who received only glucose solutions intravenously showed a negative nitrogen balance. Jonxis (1946) obtained good positive nitrogen balances by using solutions of 'capaine' (a digest of casein and lactalbumin prepared in Rotterdam) to supply a protein equivalent of about 2 g. protein per kg. per day. His subjects were suffering from only moderate degrees of food intolerance. Some reactions following the administration of 'amigen' have been reported, but later observers (Dodd and Rapoport, 1946) were able to give it for long periods to infants without the occurrence of reactions. They found, however, that thrombo-phlebitis at the site of the injection was often troublesome.

The present report* concerns a trial of a British enzymic digest of casein, 'casydrol', allocated by the Medical Research Council to the Children's Hospital, Birmingham, for intravenous administration to infants. The biological efficiency of the material had been tested previously and it had been given to adults intravenously without the occurrence of reactions.

* Part I of a report prepared for the Medical Research Council's Committee on the Protein Requirements of Infants.

Fluid, Calorie, Protein, and Mineral Requirements

The aim of parenteral therapy is to supply adequate fluid and salts and at least maintenance requirements of calories and protein. Solutions of hydrolysed casein provide a mixture of polypeptides and amino acids likely to be well utilized, so that nitrogen equilibrium may be maintained if they are given in sufficient quantities. Casein is a better source of the sulphur-containing amino acids and of tryptophane than plasma (Williamson, 1944; Brand, Kassel and Saidel, 1944; Block and Bolling, 1944) and it is more easily obtained. The content of sodium and potassium in casein hydrolysate solutions is better balanced for the needs of the infant than it is in plasma. Sterile solutions of hydrolysed casein in sealed bottles can be stored indefinitely. Since the metabolic output is often raised under the stress of disease it may not be desirable or possible to cover the losses completely during the acute phase of an illness. If wasting is partially arrested, full repair can await a stage of convalescence at which oral feeding is well tolerated. The calorie value of the solutions at present available for intravenous infusions is low for two reasons, (a) stronger solutions of glucose and protein digests are irritative to the vein, and (b) emulsions of fat which would supply more calories have not yet been prepared on a large scale for intravenous use. It was decided to give infants requiring continuous intravenous infusions a total fluid intake of about 150 ml., containing 45 calories and at least 2·2 g. of protein equivalent per kg. body weight per day (i.e. 2½ oz., 20 calories, and 1 g. of protein equivalent per lb. body weight per day). These amounts are contained in 'casydrol' (1·7-2·5 per cent.) in 5 per cent. glucose solution given at a rate of about 6 ml. per kg. (or 3 ml. per lb.) each hour. Blood and plasma which are sometimes given as part of the daily infusion, have a somewhat lower calorie value (20 instead of 28 per 100 ml.).

The mineral requirements of the infant are met by a maintenance infusion of 'casydrol' and glucose as described above unless gross extrarenal losses are being sustained during the course of treatment, for example, in severe gastro-enteritis. If treatment is very prolonged, supplements of calcium may be required (Rapoport, Dodd, Clark, and Syllm, 1947). Table 1 shows the amounts of sodium, potassium, and calcium in 'casydrol' glucose, 'amigen' glucose, and plasma glucose solutions compared with those in human milk and in cow's milk. The

TABLE 1

COMPOSITION OF SOLUTIONS OF CASEIN HYDROLYSATE AND PLASMA COMPARED WITH HUMAN AND COW'S MILK

Fluid	Na. mg. per 100 ml.	K. mg. per 100 ml.	Ca. mg. per 100 ml.	Approximate calories per 100 ml.	Protein equivalent g. per 100 ml.
'Casydrol' 2½ per cent. in 5 per cent. glucose ..	117 or less	42±	1	28	About 2·25
'Amigen' 2½ per cent. in 5 per cent. glucose ..	52	7·5	10	29	1·9
Plasma 50 per cent. in 5 per cent. glucose ..	167	10	5	30	2·5
Human milk	11	48	34	70	1·0–1·5
Cow's milk	61	154	122	70	3·0–3·5

calorie values and the percentage protein equivalent are also shown. Since the amount of sodium contained in a continuous daily infusion of 'casydrol' may be equivalent to as much as 1·5-2·0 g. sodium chloride for a 10 lb. infant per day, and more than this is given if the infusion is being supplemented by blood or plasma, it is necessary to watch for signs of salt retention, such as oedema, and to regulate the therapy accordingly. Half-strength plasma contains more sodium and less potassium, while 2½ per cent. 'amigen' contains less of both these electrolytes than 2½ per cent. 'casydrol.' An infusion fluid can be used more freely if the salt content is low, and therefore a preparation of 'casydrol' with a sodium content similar to that of 'amigen' would be preferable for administration to infants.

Method of Administration

At the beginning of our investigation 'casydrol' was available only as a 5 per cent. solution in 5 per cent. glucose. In order to give the estimated maintenance requirements of protein (2·2 g. per kg. per day) to infants, one-third of the solution together with two-thirds of 5 or 10 per cent. glucose were used, thus diluting the strength of the 'casydrol' to 1·7 per cent. This method was chosen instead of alternating 'casydrol' glucose with simple glucose solutions because it was thought (1) that the weaker dilution might be less irritating to the veins, and (2) that the utilization of a minimal daily nitrogen intake might be higher if it were given evenly throughout the twenty-four hours rather than in larger amounts for shorter periods.

The use of the weak 'casydrol' solution proved to be satisfactory in so far as no difference was observed between the 'life' of veins which received it and those which received glucose solutions alone. This finding is contrary to the experience of observers using 5 per cent. 'casydrol' solutions for infants. The 1·7 per cent. solution given at the rate of 150 ml. per kg. per day supplies only a minimal protein intake and it was found that the volume of the infusion sometimes fell short of this amount owing to technical difficulties. Accordingly, it was decided to increase the strength to 2·5 per cent. The manufacturers supplied a 2½ per cent. 'casydrol' in 5 per cent. glucose solution which could be given directly, thus avoiding the risks from contamination when mixing the solutions. The 'maintenance' infusion containing 'casydrol' was never given to patients until any dehydration present had been relieved by glucose and salt solutions and a free flow of urine had been established.

Apparatus. The apparatus used for the infusion was modified as the investigation proceeded. At first the reservoir consisted of an open flask (100-250 ml.) covered with gauze and the only precautions against contamination were (1) careful aseptic technique at times when the flask was being refilled, and (2) a complete change of apparatus every twenty-four hours. Warnings of the grave risks accompanying the administration of amino acid solutions by the open method have been given by Dodd and Rapoport (1946). In 1947 Walton designed a closed apparatus suitable for administering continuous infusions to infants and this technique has been adopted. The apparatus has been used with satisfactory results and occasional bacteriological tests of the infusion fluid from various parts of the system have always shown it to be sterile. The open method was used in forty-six, and the closed in fifteen cases.

Vitamin Supplements

Patients receiving intravenous infusions need vitamin supplements, and these should be given in optimum doses in order that any tendency to a deficiency may be overcome. Our patients have received vitamins intramuscularly and a single injection daily has usually been given. The following may be safely mixed in a syringe immediately before administration:

'Beminal' 1 ml.	Aneurin, 10 mg. Riboflavin, 0·5 mg. Nicotinic acidamide, 25 mg. Pyridoxin, 0·5 mg. Pantothenic acid, 0·5 mg.
Ascorbic acid, 50-100 mg.	
'Synkavit' 0·5-1 ml.	Tetra-sodium salt of menaphthone diphosphate, 5-10 mg.

Patients suffering from severe infection and those receiving prolonged treatment have also been given

Vitamin A, as ' davitamon A. forte ' 0·5 ml., on alternate days, supplying 30,000 units per dose. Crude liver extract combined with Vitamin B preparations such as ' plexan ' and ' heparglandol ' (2 ml. alternate days) have sometimes been used instead of the ' beminal,' particularly for patients with clinical enlargement of the liver.

Antibiotics

All patients receiving parenteral fluids should be given penicillin with or without a sulphonamide preparation as a prophylactic measure against infection, and in many cases antibiotics are specifically indicated as part of the treatment of the primary disease. Penicillin has been given to our patients intramuscularly (10,000 units per kg. per day in divided doses at three- to six-hourly intervals). When oral feeding has been resumed penicillin has sometimes been given by mouth (240,000-360,000 units per day to the smaller babies according to their age). Sulphonamides have been administered intravenously and subcutaneously. Since these drugs must not be mixed with infusions of ' casydrol ' or plasma, it has become customary to give them subcutaneously. A 5 per cent. solution of sulphadiazine in lactate-ringer (or saline) solution (Forbes, Donnell, and Herweg, 1947) is well tolerated, and the dose is 0·1-0·15 g. per kg. body weight per twenty-four hours in divided doses at twelve-hourly intervals. This method of administration has been found to maintain high concentrations in the blood. The levels have been checked frequently and the dose modified accordingly. When oral feeding has been resumed sulphadiazine has been continued by mouth, the dose being raised to 0·3 g. per kg. body weight per twenty-four hours in divided doses three-hourly or four-hourly according to the intervals used for feeding.

Subjects for the Investigation

Sixty-one patients were selected for the trial of ' casydrol ' all suffering from conditions which had necessitated the withdrawal of oral feeding for periods of several days. At the beginning of the investigation ' casydrol ' was given to patients who were already receiving intravenous infusions and were in the terminal stages of an illness; this was not expected to affect the course of their disease (group A, three patients). Other patients were only given occasional infusions of ' casydrol ', so that results from them can be used to judge tolerance to the injection but not other effects (group B, twenty patients). The remaining thirty-eight patients who received ' casydrol ' intravenously were given amounts which reached the estimated requirements for maintenance infusions. In some, however, the infusions were continued for short periods only, either because of rapid improvement allowing a change over to oral feeding, or because they died (group C, twelve patients). Group D (twenty-six patients) were treated systematically for several days and their progress has been examined in detail, the salient points being shown in table 3. The infants have been arranged under the following clinical headings:

1. Those with congenital obstructions of the alimentary tract.
2. Those suffering from peritonitis and paralytic ileus.
3. Those suffering from severe gastro-enteritis.

Classifying the sixty-one subjects of this investigation according to these categories, table 2 shows the type of treatment given (Groups A, B, C, D) and the rates of recovery or death.

Results

There have been no general reactions (of the type to indicate pyrogenic activity in the fluid being administered) in the sixty-one infants to whom continuous intravenous infusions of ' casydrol ' have been given. A more rapid injection by syringe was given on two occasions to one small infant (C.K., No. 5) because her veins were not suitable for continuous intravenous infusion. The child became temporarily collapsed as the result of each injection, but there were no permanent effects. After this experience rapid administration of ' casydrol ' was no longer practised. Warnings against this method are to be found in the literature (Kozoll, Hoffmann, and Meyer, 1945). There has been no apparent increase in the incidence of local reactions at the site of injections since maintenance infusions of ' casydrol ' solution have been used in place of glucose solutions alone or glucose solutions and plasma. The veins of an infant vary in their tolerance to continuous intravenous infusions, but they can be used for at least forty-eight hours and

TABLE 2

CLASSIFICATION OF SIXTY-ONE INFANTS RECEIVING ' CASYDROL ' SOLUTION INTRAVENOUSLY

Disease	Unsystematic Administration				Systematic Administration			
	Group A. Moribund		Group B. Interrupted Treatment		Group C. Short Treatment		Group D. Long Treatment	
	Recovered	Died	Recovered	Died	Recovered	Died	Recovered	Died
1. Congenital obstructions	0	1	0		0	1	0	2
Pyloric stenosis ..					1	1		
2. Peritonitis with paralytic ileus	0	1	2	4	1	0	5	2
3. Severe gastro-enteritis ..	0	1	3	10	7	1	14	3
Total	0	3	5	15	9	3	19	7

TABLE 3

COURSE OF TWENTY-SIX INFANTS RECEIVING INTRAVENOUS INFUSIONS OF 'CASYDROL'

Group	Disease	No.	Name	Age	Diagnosis	Treatment				Result		
						Parenteral infusions		Antibiotics S. = Sulphonamides P. = Penicillin O. = Oral i.m. = Intramuscular Route i.v. = Intravenous Route s.c. = Subcutaneous Route	Surgical	Recovery Stay in Hospital	Death Length of illness	Necropsy Findings
						Alone	+ Oral feeding					
1	CONGENITAL OBSTRUCTION OF ALIMENTARY TRACT	1	R.D.	2 days	Meconium ileus	three days No blood given Plasma given	two days	S. only given terminally No P. given	Caecostomy drained three days after operation	—	8 days	General Peritonitis. Meconium Ileus. Cystic fibrosis of pancreas.
		2	L.R.	5 days	Tracheo-oesophageal fistula	four days Plasma given No blood given	three days	S. i.v. P. i.m.	Anastomosis satisfactory. Healed at p.m.	—	7 days	Gross haemorrhage into bowel. Haemorrhagic diathesis.
2	PERITONITIS WITH PARALYTIC ILEUS	3	W.B.	10 days	(a) Umbilical sepsis (b) Peritonitis (c) L. otitis media	(i) two days (ii) three days Plasma and blood given	(i) four days (ii) seven days	S.o. (Good blood levels) P. i.m.	—	—	31 days	Obstruction with bands + local perforation. Unresolved pneumonia. Small abscesses of lung. Pinhead abscess of kidney.
		4	J.J.	2 weeks	(a) Umbilical sepsis (b) Peritonitis	three days Plasma given No blood given	—	S.o. (No blood levels). P. i.m.	—	—	3 days	Peritonitis. Ulcerative colitis. Terminal pneumonia.
		5	C.K.	6 weeks	Peritonitis ? Due to appendix abscess	eighteen days (closed) Plasma and blood given	seven days	S. i.v.→o. (Poor blood level) S.c.→o. (Good blood levels) P. i.m.	—	85 days	—	
		6	K.J.	8 weeks	Peritonitis following intussusception	—	(i) ten days (ii) two days Plasma and blood given	S. i.v.→o. P. i.m.	(i) Reduction of intussusception. (ii) Repair of wound and division of adhesions.	38 days	—	—
		7	D.J.	11 weeks	Peritonitis ? following strangulated hernia	five days (closed) Plasma and blood given	three days	S. S.c.→o. P. i.m.	—	47 days	—	—
		8	G.L.	5½ mths.	? Peritonitis associated with gastro-enteritis	eight days (closed) No plasma given Blood given	sixteen days	S. o.→S.c.→o. (High blood levels) P. i.m.	—	52 days	—	—
		9	P.P.	8 months	Peritonitis following appendix abscess	(i) three days (ii) two days Plasma and blood given	(i) six days (ii) five days	S. i.v.→o. P. i.m.	(i) Drainage (sixth day) (ii) Ileostomy. Relief of obstruction from adhesions (seventeenth day). (iii) Ileostomy closed (twenty-second day).	52 days	—	—
3	GASTRO-ENTERITIS	10	P.H.	12 days	(a) Neonatal septicaemia (b) Gastro-enteritis (c) Peritonitis (d) Stomatitis	seven days Plasma given No blood given	seven days	S. i.v.→o. P. i.m.	—	—	21 days	Healing cerebral injury. General peritonitis. Enteritis. Otitis media. Toxic renal changes.
		11	A.F.	3 weeks	(a) Neonatal septicaemia. (b) Gastro-enteritis. (c) Otitis media	two days Plasma given No blood given	one day	S. i.v.→o. P. i.m.	Bilateral myringotomy. Pus both.	31 days	—	—

Group	Disease	No.	Name	Age	Diagnosis	Treatment: Parenteral infusions — Alone	Treatment: Parenteral infusions — + Oral feeding	Treatment: Antibiotics (S. = Sulphonamides, P. = Penicillin, O. = Oral, i.m. = Intramuscular Route, i.v. = Intravenous Route, s.c. = Subcutaneous Route)	Treatment: Surgical	Result: Recovery — Stay in Hospital	Result: Death — Length of illness	Result: Necropsy Findings
	GASTR	11	A.P.	3 weeks	(a) Neonatal septicaemia. (b) Gastro-enteritis. (c) Otitis media	two days	one day Plasma given No blood given	P. i.m.	Bilateral myringotomy. Pus both.	31 days	—	—
3	GASTRO-ENTERITIS	12	W.H.	5 weeks	Gastro-enteritis	three days	three days (closed) Plasma given No blood given	S. o. P. o.	—	22 days	—	—
		13	J.B.	6 weeks	Gastro-enteritis associated with cholangitic biliary cirrhosis	one day	nine days Plasma and blood given	P. i.m. No. S. given	—	—	16 days	Enteritis. Purpura. Cholangitic biliary cirrhosis.
		14	M.N.	6 weeks	Gastro-enteritis	—	four days (closed) No plasma given Blood given	S. o. P. o.	—	54 days	—	—
		15	K.U.	9 weeks	(a) Gastro-enteritis. (b) Otitis media.	one day	three days Plasma given No blood given	S. i.v.→o. P. i.m.→o.	Bilateral myringotomy. L. pus.	46 days	—	—
		16	M.S.	10 weeks	(a) Gastro-enteritis. (b) Bilateral mastoiditis.	two days	three days Plasma given No blood given	S. o. P. o.	Bilateral myringotomy. Bilateral mastoidectomy 21 days later.	58 days	—	—
		17	M.K.	14 weeks	Intercurrent infection: Gastro-enteritis.	one day	two days Plasma given No blood given	S. o. P. i.m.→o	—	26 days	—	—
		18	J.B.	4 months	(a) Gastro-enteritis (b) Respiratory infection.	three days	two days Plasma given No blood given	S. o. P. i.m.→o.	—	17 days	—	—
		19	S.G.	4 months	Intercurrent infection: (a) Gastro-enteritis. (b) Respiratory infection.	one day	twelve days Plasma given No blood given	S. o. P.i.m.	—	22 days	—	—
		20	A.S.	4 months	Gastro-enteritis	one day	two days (closed) Plasma given No blood given	S. i.v.→o. No P. given	—	27 days	—	—
		21	C.W.	4 months	Gastro-enteritis	one day	two days No plasma given No blood given	S. o. (Poor blood levels) P. i.m.	—	15 days	—	—
		22	S.R.	5 months	Intercurrent infection: Gastro-enteritis	two days	five days Plasma given No blood given	S. o. P. i.m.→o.	Bilateral mastoidectomy. No mastoiditis.	16 days	—	—
		23	K.B.	5½ months	Gastro-enteritis	two days	three days Plasma given No blood given	S. o. P. i.m.	—	24 days	—	—
		24	L.H.	7 months	(a) Gastro-enteritis (b) Respiratory infection	one day	three days Plasma given No blood given	S. o. P. i.m.	—	32 days	—	—
		25	R.M.	9 months	Intercurrent infection: Gastro-enteritis	three days	six days Plasma and blood given	S. o. P. i.m.	Bilateral mastoidectomy.	—	9 days	Bilateral mastoiditis. Terminal pneumonia. Marasmus.
		26	S.S.	10 months	(a) Gastro-enteritis. (b) Pink disease.	—	six days Plasma given No blood given	S. o. P. i.m.	—	28 days.	—	—

have often been used for three or four days continuously.

Only one infant who had been given infusions of 'casydrol' showed evidence at necropsy that the cause of death was likely to have been associated with the infusion. Septic thrombo-phlebitis (a complication of intravenous therapy of any kind) had occurred and multiple abscesses were present in the lungs. The child was admitted suffering from gastro-enteritis and death occurred thirteen days later from staphylococcal septicaemia.

Pyaemia was found in three other cases, but sites of infection were present which might have led to septic embolism. The open method was still being used at the time that these four patients were being treated.

Progress of twenty-six cases (Group D). Table 3 shows the cases divided into the three clinical groups which were used in Table 2. It will be seen that there were two cases of congenital obstruction of the alimentary tract, seven cases of peritonitis with paralytic ileus, and seventeen cases of severe gastro-enteritis. Supportive measures with parenteral feeding are a corollary to surgical treatment in treating congenital obstructions of the alimentary tract, while the treatment of infection is of primary importance in peritonitis and gastro-enteritis. These three aspects of treatment have therefore been stressed in reviewing the progress of our patients. Table 3 shows that in one case (No. 5) parenteral infusions were the sole source of nutrition for as long as eighteen days and that they were used to supplement the oral intake for a further period of seven days. Such prolonged treatment is not usually required, and the duration of parenteral therapy in the other cases varied from one to eight days for complete, and from one to sixteen days for supplementary intravenous infusions. There were seven deaths, a mortality rate of 27 per cent. Two of the deaths occurred in patients who had congenital obstruction of the alimentary tract, and both babies had made satisfactory progress during the early phase of post-operative treatment. Necropsy findings show that one died from general peritonitis and the other from an acute haemorrhagic diathesis. It is possible that these conditions might have been prevented by more systematic treatment; in the one, by the administration of antibiotics in the early days after operation, and in the other by small blood transfusions and continuation of Vitamin K supplements for a longer period. Surgical treatment had been successful in both cases. Two deaths occurred in the infants suffering from peritonitis and three in those suffering from severe gastro-enteritis. The clinical course and the necropsy findings in these patients suggest that death from the primary diseases could not have been prevented by treatment. Case 3, who had umbilical sepsis, was one of those showing a terminal miliary spread of infection which might have been introduced by the infusion fluid, or which might equally well have been due to the primary infection.

Treatment and progress of seven cases. Figs. 1 to 7 illustrate the treatment of cases 5, 7, 9, 10, 12, 20, and 22. As is shown in table 3 cases 5, 7, and 9 were infants suffering from peritonitis and paralytic ileus while the remainder were babies with gastro-enteritis.

The construction of figures, together with systematic records of the vitamin supplements and antibiotics which are being given, are valuable aids to efficient treatment. It has been our practice to keep daily records of the intake on a table which is a modification of the one described by Dodd and Rapoport (1946).

CASE No. 5. C.K. This infant aged six weeks and weighing 6 lb. 10 oz. was admitted with a history of vomiting for one week, and abdominal distension and constipation for five days (fig. 1). On examination the abdomen was found to be grossly distended, and peritonitis of unknown etiology was diagnosed. The patient was slightly dehydrated and was lethargic. She had a raised pulse rate and became pyrexial. Surgical interference was not advised.

Penicillin was given by the intramuscular, and sulphadiazine by the intravenous routes. Infusions of plasma and glucose were given to relieve dehydration, and later 2½ per cent. 'casydrol' solution with 5 per cent. glucose plus small blood and plasma transfusions were substituted according to the schedule of her requirements. Oral feeding was withheld, but sulphadiazine was given by mouth on the fourth day. The infant's general condition improved in response to treatment, but signs of peritonitis were persistent. The baby was hungry and on the eleventh day oral feeding was attempted, but it had to be discontinued on the thirteenth day owing to increasing abdominal distension. The sulphonamide level in the blood had only been of the order 3 to 7 mg. per 100 ml., and in order to raise it subcutaneous administration of sulphadiazine was begun on the fourteenth day. The level on the sixteenth day was found to be 15·5 mg. per 100 ml. On the twenty-first day bowel movements were resumed and the abdominal distension began to subside. Subsequently, oral fluids were well tolerated and milk feeds were introduced slowly. Food was badly tolerated and the baby became extremely marasmic, weighing only 5 lb. 11 oz. on the thirty-fourth day. Later she tolerated food well, and was fed according to a scheme for marasmic infants which will be described in a subsequent paper (Young, Bishop, Hickmans, and Williams, 1949). She was discharged on the eighty-fifth day weighing 7 lb. 7 oz. and continued to make good progress at home. When seen again at the age of nine months she seemed to be a normal healthy baby and weighed 19 lb.

CASE No. 7. D.J. This infant aged 11 weeks and weighing about 10 lb. was admitted with a history of vomiting of increasing severity and of constipation for two days (fig. 2). A lump in the groin had been noted for one day. On examination there were signs of acute abdominal obstruction

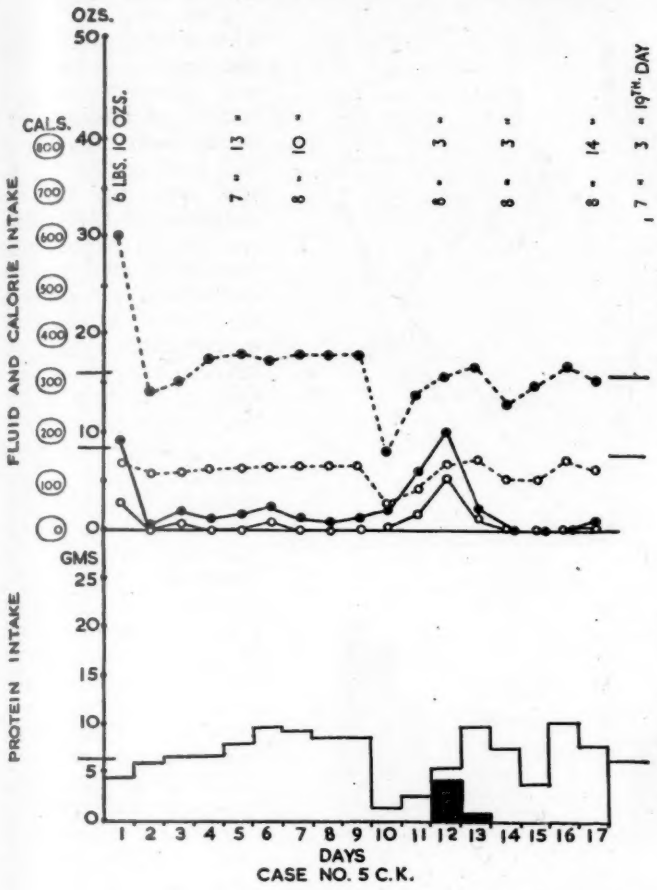

FIG. 1.

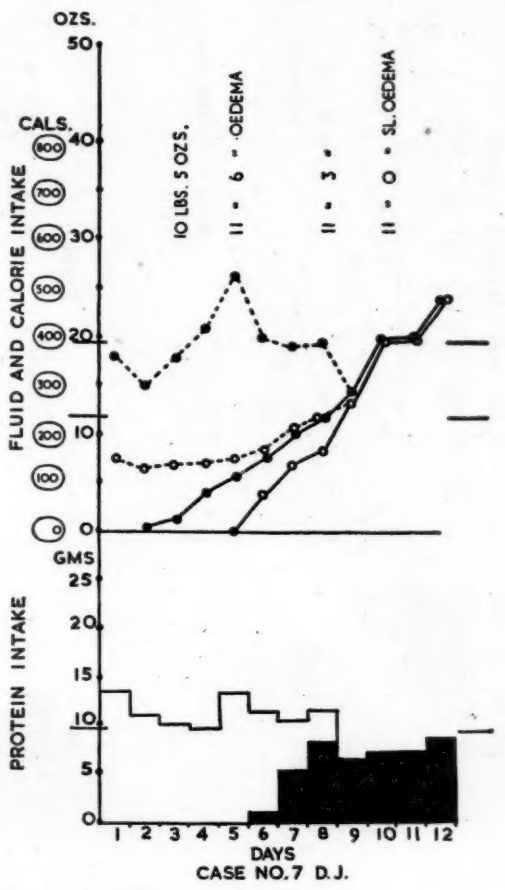

FIG. 2.

(See footnote for key to charts)

●——● Daily fluid intake in oz. (oral).
●·····● Daily fluid intake in oz. (oral + intravenous).
○——○ Daily calorie intake (oral).
○·····○ Daily calorie intake (oral + intravenous).
Black block Daily protein intake in g. (oral).
White block Daily protein intake in g. (intravenous).
The horizontal lines on the vertical scale of the figures at three levels represent from above downwards the estimated maintenance requirements of fluid (2½-2¼ oz. per lb.), calories (20 per lb.), and protein (1 g. per lb.).

possibly due to a strangulated hernia which had reduced itself. The vomits consisted of thick mucus with a faecal odour. The patient was pyrexial and had a raised pulse rate. There were signs of shock at the time of admission. Surgical treatment was not advised.

Penicillin was given by the intramuscular, and sulphadiazine by the subcutaneous, routes. The stomach contents were aspirated by a Ryle's tube. Infusions of plasma and glucose were given until dehydration had been relieved on the second day, and subsequently those of 2½ per cent. 'casydrol' in 5 per cent. glucose with the usual additions of blood transfusions and of vitamin supplements were substituted. The child's condition remained critical for two days. On the third day there were signs that the obstruction was relieved. A high sulphonamide level of 30 mg. per 100 ml. in the blood was reached on the second and fourth days. It fell to 16 mg. per 100 ml. on the fifth day. On the fourth day the general condition had greatly improved, but the infant had become oedematous. Oral fluids were gradually substituted for the intravenous infusion and were well tolerated. Intravenous infusions were therefore discontinued on the eighth day, although only a minimal intake was being provided by the diet. Later the quantity of food was increased, and the patient, now weighing 11 lb. 4 oz., was discharged on the forty-seventh day.

CASE NO. 9. P.P. This baby aged five and a half months, and weighing about 14 lb., was admitted with a history of copious vomiting and of constipation for five days (fig. 3). On examination the abdomen was found to be distended and 'doughy.' The patient was pyrexial and had a raised pulse rate. She was moderately dehydrated.

Antibiotics were prescribed. Intravenous infusions for the relief of dehydration and for maintenance were given as in Cases 5 and 7. The signs of peritonitis persisted and laparotomy was performed on the sixth day when a large purulent effusion was found. The appendix was thought to be the origin of the suppuration but was not located. The

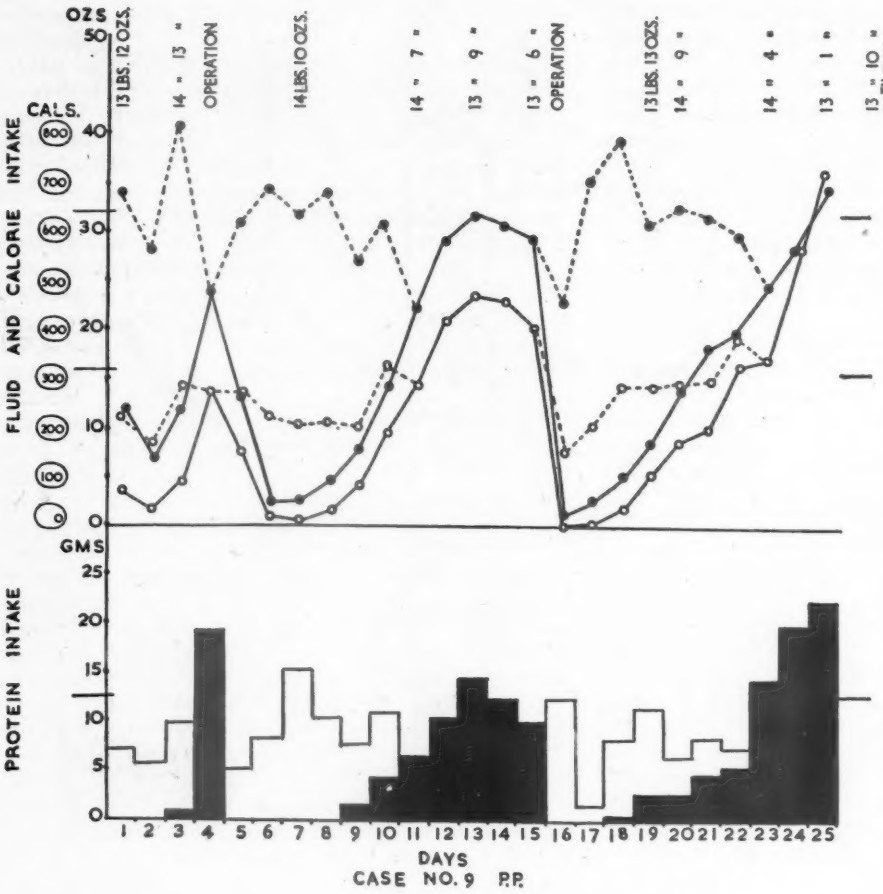

FIG. 3.

abdomen was drained and discharged freely during the post-operative period. Culture of the pus yielded Bact. coli and a streptococcus. Paralytic ileus persisted after operation and it was treated by gastric suction, chemotherapy, and continuation of intravenous infusions. As may be seen from fig. 3, however, 'maintenance' requirements of calories and protein were not always reached. On the tenth day (i.e. four days after operation) bowel movements were resumed and oral fluids were allowed, and by the thirteenth day, oral feeding was sufficient to provide an adequate fluid intake. On the seventeenth day, there was a sudden recurrence of vomiting and abdominal distension. A second laparotomy was performed and the obstruction was found to be due to adhesions. These were divided and an ileostomy was performed, which began to function after two days and was closed after five days. Oral feeds were introduced, but it was not until the twenty-third day, and six days after the second operation, that intravenous infusions could be discontinued. Progress thereafter was satisfactory and the patient was discharged in good health on the fifty-second day.

CASE NO. 10. P.H. This infant, twelve days old and weighing 7 lb., was admitted with a history of feeding difficulties from birth. Stools had been of the starvation type (fig. 4). On examination the patient was found to be toxic and dehydrated, but the only abnormal signs were slight umbilical sepsis and a haematoma over the left occipital bone. General neonatal infection was suspected.

Antibiotics were prescribed. Infusions were given to relieve dehydration and oral feeding was attempted, but was badly tolerated. Accordingly, a maintenance infusion with the usual additions of plasma was given. There was never any improvement in response to treatment. Generalized oedema developed following a plasma transfusion and a total salt intake of 2 g. on the fifth day. Further attempts were made to feed the child by mouth but without success. His condition deteriorated and he died on the sixteenth day. Post-mortem examination revealed a cerebral birth injury and multiple infections (see table 3).

CASE NO. 12. W. H. This infant aged five weeks and weighing 7 lb. 8 oz., was admitted with a history of vomiting for five days and diarrhoea for two days (fig. 5). On examination the patient was found to be grossly dehydrated with signs of circulatory failure. Primary gastro-enteritis was diagnosed.

Antibiotics were prescribed. Infusions were given to relieve dehydration and after forty-eight hours the child's general condition was greatly improved. The diarrhoea had persisted, however, and it was decided to withhold food and to give the maintenance infusion containing 'casydrol.' This was continued between the second and fifth days. By this time the diarrhoea had subsided and oral feeding was well tolerated. The patient, weighing 8 lb. 6 oz., was discharged well on the twenty-second day.

CASE NO. 20. A.S. This infant was four months old and weighed 7 lb. 8 oz. on admission (fig. 6). His birth weight had been 6 lb. 3 oz., but there had been

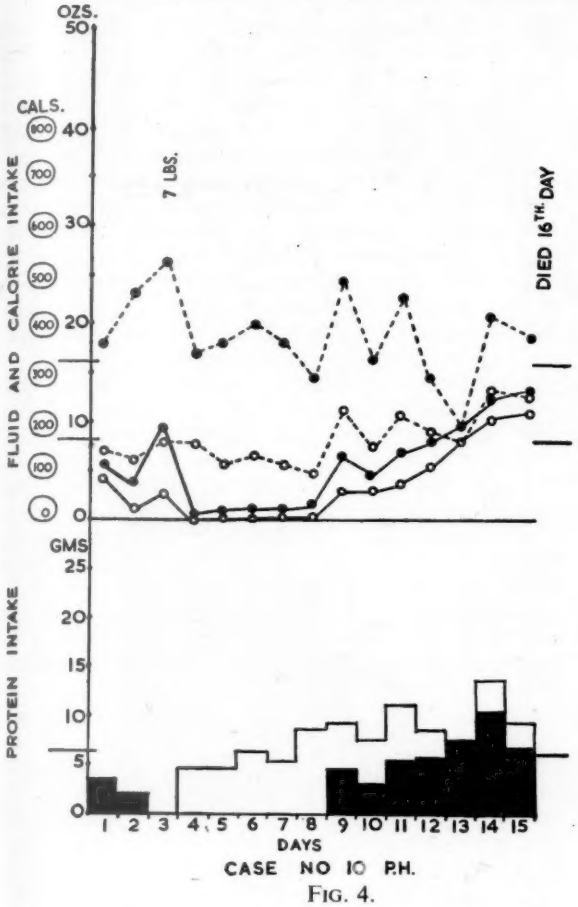

FIG. 4.

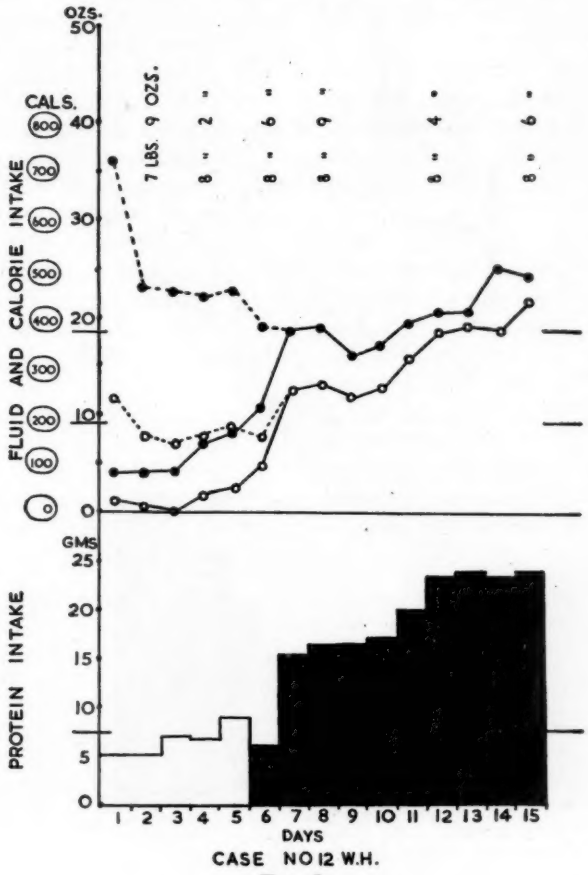

FIG. 5.

feeding difficulties since birth and very little weight gain during four months. The infant had had a previous attack of diarrhoea which was treated in hospital and he had made good progress. The diarrhoea had recurred at home and had continued for more than a week. On examination the patient was found to be very dehydrated and extremely wasted. The diagnosis was gastro-enteritis and marasmus.

Chemotherapy was prescribed and dehydration was relieved by infusions of plasma and glucose solutions followed by a maintenance infusion containing ' casydrol.' Oral feeding was introduced on the third day. Contrary to expectations, this infant made uninterrupted progress and food was well tolerated. He was fed according to a schedule for marasmic infants (Young, et al., 1949). He was discharged, weighing 8 lb. 2 oz., on the sixteenth day.

CASE NO. 22. S.R. This baby of five months was admitted for diagnosis of a recurring rash and oedema of the face since the age of two months (fig. 7). The patient contracted diarrhoea while in hospital and became dehydrated. No definite signs of aural infection were found, but mastoiditis was suspected and mastoidectomy performed.

Antibiotics were prescribed, and dehydration was relieved by an intravenous infusion during the first day. Maintenance infusions containing ' casydrol ' were continued from the second to the seventh day, oral feeding having been introduced on the fourth day when the diarrhoea was well controlled. The infant made uninterrupted progress, but slight oedema was noted from the second to the sixth day. The child, weighing 14 lb. 12 oz., was discharged well on the twenty-seventh day.

The first three figures illustrate the treatment of peritonitis (1) in a case of prolonged obstruction of the bowel, (2) in one who made an early recovery, and (3) in one with a relapse. There seems to be more tendency for oedema to develop in these cases than in those with gastro-enteritis, in which the extrarenal losses are usually higher. The oedema may be an inevitable complication when an accumulation of gastro-intestinal secretions from the bowel enters the circulation after the relief of an obstruction. This is probably what happened in case 7 (fig. 1) on the fourth day.

The last four charts illustrate the treatment of different types of patient with diarrhoea and vomiting. In case 10 these symptoms were associated with neonatal infection. In case 12 and case 20 they were primary, but case 20 contracted

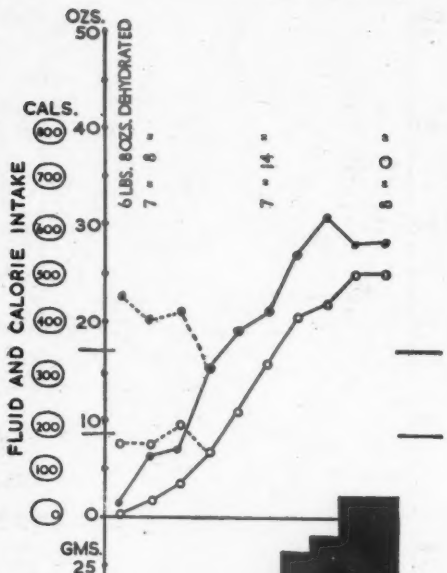

FIG. 6.

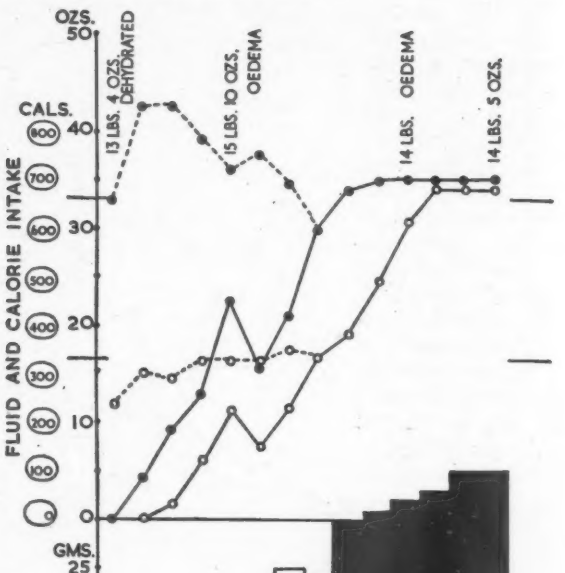

FIG. 7.

his illness when he was already in a severe state of malnutrition. Case 22 began the disease in hospital presumably from cross-infection, although the contact could not be traced.

Discussion

The advantages of giving protein digests intravenously to adult patients who cannot tolerate oral feeding have been well stressed and summarized by Magee (1948), and the need for protein is relatively greater in infancy than at later ages owing to the demands of growth. Milk protein would seem to be a good source, particularly for young infants whose natural food is milk. In disease, a mixed digest prepared from liver or meat might supply special needs. Plasma should be given only in limited amounts owing to the high content of sodium salts (in citrated preparations it may be even higher than in the circulating plasma (see table 1)), and to the inability of infants to excrete them as efficiently as older subjects (Young, Hallum, and McCance, 1941; Dean and McCance, 1947).

The results of this investigation have shown that the administration of intravenous infusions containing 'casydrol' is practicable and without danger. The benefits following its use have not been clearly demonstrated, but an impression has been obtained that very sick infants have reached convalescence in a better state of nutrition than those who were treated before these solutions were available, and that some have lived whose chances of survival through a long period of starvation would have been regarded as hopeless. The advantages may be due partly to a better balance of sodium and potassium salts (Darrow, 1946; Govan and Darrow, 1946) in the 'casydrol' infusions (see table 1) as well as to the derivatives of protein which they contain. We have noticed that anorexia (a feature frequently associated with acute abdominal conditions) has not been a symptom in the present series. The advent of penicillin and the systematic administration of vitamin supplements parenterally to patients at times when oral feeding is withheld have coincided with the present trial, and each of these factors is likely to have contributed to the results.

Emphasis has not been placed on changes in the weight of our patients during periods when they were receiving intravenous infusions. Wide fluctuations may occur but these do not bear a close relationship to 'true' body weight, because they are affected by differences in the state of hydration.

Thus patients always gain weight as dehydration is relieved, and a further gain may be due to an increase in body water with or without visible oedema. Dodd and Rapoport (1946) have claimed that gains in weight may be achieved in infants receiving parenteral fluids alone with the use of glucose, whole blood, plasma, and casein hydrolysate solutions. They have failed to stress, however, that their patients on admission were often dehydrated and that, therefore, considerable weight gains were to be expected as the body fluids were being restored. Nevertheless, these authors usually gave their patients (particularly the smaller ones) a higher daily intake of fluid, calories, and protein than the patients in our investigation were receiving, and their weights might therefore be expected to be well maintained. Dodd and Rapoport found that they were able to neglect close control of the total intake of fluid provided that care was taken to avoid an excess of salt. The preparation of hydrolysed casein (' amigen ') which they were using has a lower concentration of salt than ' casydrol ' (about half), and therefore it could be given in larger amounts with greater safety. It might be dangerous to copy their practice if ' casydrol ', as it is now prepared, were being used. The American workers also used 10 per cent. glucose solution, instead of the 5 per cent. solution which is isotonic but provides fewer calories. So far, we have had no experience of using 10 per cent. glucose solution for maintenance infusions, but if it were well tolerated by the veins it would probably be advantageous. Butler and Talbot (1944), agree with Dodd and Rapoport (1946) that it is practicable to give it to infants for continuous intravenous infusions.

In conclusion, the provision of protein digests such as ' casydrol ', suitable for intravenous use in infants, has drawn attention to our lack of knowledge concerning protein metabolism in the conditions which have been described, and nitrogen balance experiments in sick and convalescent infants might enable us to assess and fulfil their needs with greater assurance. The development of methods for preparing fat emulsions suitable for intravenous administration would provide a higher caloric intake which would spare the protein for repair. Despite the present drawbacks, infusions of ' casydrol ' have been considered valuable for cases of severe gastro-enteritis, acute abdominal conditions, and the difficult congenital abnormalities of the alimentary tract. A long period of oral starvation, on which ultimate recovery may depend, can be planned with safety, thus allowing the primary site an adequate interval of rest.

Summary

Intravenous infusions of an enzymic digest of casein (' casydrol ') with glucose have been given to sixty-one infants without any reactions being observed. Necropsy findings suggest that there was an embolic spread of infection in one case as the result of the infusion, while in three others this complication might have been due to the infusion, but was more probably due to a focus of infection already present in the body. An infusion of 2½ per cent. ' casydrol ' in 5 per cent. glucose solution was well tolerated by the veins. A ' closed ' method of administering intravenous fluids must be used to safeguard patients from the risks of contamination of the infusion.

Twenty-six infants received infusions of ' casydrol ' for a period of several days so that the treatment was likely to have affected the course of their disease, and of these nineteen survived, and seven died. Other factors, such as plasma and blood transfusions and parenteral supplements of vitamin preparations, probably contributed to the good results in the patients who recovered.

Further knowledge of the nitrogen metabolism of sick and convalescent infants is needed, so that a full use may be made of the preparations now available for intravenous administration.

The authors wish to thank Professor Sir Leonard G. Parsons and Professor J. M. Smellie for their helpful criticism and advice, and the medical staff of the Children's Hospital, Birmingham, for allowing them to work in their wards. W.F.Y. received a grant from the Medical Research Council, and Y.J.W. a Research Scholarship from the Department of Paediatrics and Institute of Child Health, while E.A.B. and W.F.Y. each held the Caroline Harrold Research Fellowship of Birmingham University during part of the time these investigations were in progress, and these awards are gratefully acknowledged. The Medical Research Council supplied a part and the manufacturers a part of the ' casydrol ' solution used in this investigation.

The co-operation of the ward sisters has been invaluable, and Mr. J. G. Williamson, the photographer, has been of great assistance in preparing the diagrams.

The special preparations referred to in this paper were supplied by the following :

' Amigen ' by Mead Johnson & Co., U.S.A.; ' casydrol ' by Genatosan Ltd.; ' beminal ' by Warner Bros., U.S.A.; ' synkavit ' and ' heparglandol ' by Roche Products, Ltd.; ' plexan ' by Glaxo Laboratories, Ltd.; and ' davitamon A. forte ' by Organon Laboratories, Ltd.

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ORAL PENICILLIN IN THE NEWBORN

BY

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This investigation was initiated to determine the optimal dose of oral penicillin required to give a satisfactory penicillin blood level in infants under a month old and to compare the relative efficacy of penicillin and sulphathiazole paste in the treatment of minor skin lesions in infants during the neonatal period. The obvious advantages of penicillin over other drugs are counterbalanced by the discomfort of intramuscular injections and the possible danger of infection in the injection site. Oral penicillin is clearly preferable to intramuscular injection provided adequate blood levels are attained.

Previous Investigations

When this investigation was commenced early in 1947, two reports had appeared (Henderson and McAdam, 1946, and Buchanan, 1946) on oral penicillin in infants. Both showed that adequate and sustained blood penicillin levels could be obtained in this way. Since then a number of other favourable reports have appeared (Markowitz and Kuttner, 1947; Hoffman, Hofer, and Gordon, 1948; Lapin, 1948; Suchett-Kaye and Latter, 1947). Early investigations had shown (Florey, M. E., and Florey, H. W., 1943; Abraham, Chain, Fletcher, Gardner, Heatley, Jennings, and Florey, 1941; Rammelkamp and Keefer, 1943) that with adults a proportion of the penicillin given by mouth was absorbed, but that this was small. Later investigations have shown that with very high doses of penicillin given orally, a reasonable blood level can be maintained in adults. McDermott et al. (1945) stated that about 20 per cent. of the penicillin given orally to adults was excreted in the urine, whereas following intramuscular penicillin about 60 to 70 per cent. was excreted. They conclude that since about one-third of the oral penicillin is absorbed, in order to reach comparable blood levels the oral dose must be at least three times the intramuscular dose, and, to cover those cases in which the absorption is less than 33 per cent., it is better to give five times as much.

Seeberg et al. (1946) have similarly shown that in cats urinary excretion is five times greater after intramuscular than oral penicillin with equivalent amount. They further showed that the duodenum and small intestine were the areas of greatest absorption, and the colon the area of greatest destruction of penicillin.

Two explanations have been suggested for the lower blood penicillin levels with oral therapy.

(1) Gastric acidity inactivates or destroys part of the penicillin.

(2) Absorption occurs mainly in the duodenum and small intestine; what is not absorbed is destroyed by penicillinase-producing organisms in the large intestine, little or none being excreted in the faeces.

A third possibility has been advanced by Free et al. (1945) that after oral penicillin some is destroyed or stored in the liver.

If the first explanation were correct, protection from gastric acidity should increase the amount of penicillin absorbed. A number of investigators have reported on the effects in adults of giving oral penicillin with antacids, buffers, oils, and in capsules, with conflicting results. Seager (1946) obtained higher levels with antacids than with tap-water. György et al. (1945) showed that higher levels could be obtained with trisodium citrate buffered penicillin than with aqueous penicillin. On the other hand, McDermott et al. (1946) found that results with penicillin in plain water were as good as penicillin given with various antacids. Further, in achlorhydric patients the absorption of oral penicillin was little or no better than in normal subjects. Oberst et al. (1946) and Free et al. (1945) also concluded that simple aqueous penicillin gave as good results as penicillin with antacids. In children Cohlan et al. (1948) obtained higher levels with trisodium citrate buffered penicillin than with unbuffered penicillin, whereas in infants buffering made no difference to the levels. They found that when penicillin was incubated in vitro with the gastric juice of infants there was little destruction of penicillin, whereas almost complete destruction occurred when the gastric juice of children was substituted. They ascribed this difference to the greater acidity of the latter. It has been noted, however, that higher levels are obtained when penicillin is given before meals. Reisman et al. (1947) found no difference between penicillin in saline and buffered penicillin in children, but noted that levels were best when penicillin was given half an hour before or three hours after a meal. Markowits and Kuttner (1947) gave oral penicillin to children between six and fourteen years, half an hour before breakfast, just before breakfast, and immediately after meals. The blood levels were highest in the first series, only slightly lower in the second, and very low and irregular in the third. This confirmed previously reported observations.

Present Investigations; Penicillin Blood Levels

First Series. This comprised forty-two cases and seventy-nine blood levels were determined. The dose given was 120,000-160,000 units per twenty-four hours.

In order to be certain of attaining adequate levels of penicillin in the blood, a massive dose was first used: 20,000 units were given three- or four-hourly, depending on the number of feeds, giving a total dosage of 120,000 or 160,000 units per twenty-four hours. The dosage per lb. consequently varied widely with the birth weight and was between 13,000 and 40,000 units. The ordinary sodium penicillin tablets, not containing citrate, were used, dissolved immediately before use, and given in a teaspoon of water just before the feed. Occasionally, if the penicillin was refused, the solution was mixed with milk, and given before the feed.

For the estimation of the blood penicillin level, blood was withdrawn from the heel with the usual precautions one hour after, and again three or four hours after the dose had been given, depending on the time of feed. In all cases the estimation was performed after the infant had been on penicillin for twenty-four to forty-eight hours, when blood levels would be expected to be higher than those following a single dose, since in many cases there is an appreciable amount of penicillin in the blood three or four hours after a dose. The method of estimation was similar to that of Fleming (1947), using a strain of Staph. aureus which has been in continuous use for this purpose. It is sensitive to a penicillin concentration of 0·031 units per ml. Serial dilutions of the serum to be estimated were made in small 2 in. by $\frac{3}{8}$ in. test tubes, using a glucose serum broth containing phenol red as indicator. To 5 ml. of this medium was added 20 c.mm. of an eight-hour culture of the test organism. Where sufficient serum was available, a second series of intermediate dilutions was also done. A control series, containing known dilutions of

TABLE 1

PENICILLIN LEVELS (DOSE: 20,000 UNITS EVERY THREE OR FOUR HOURS) IN THE NEWBORN

Penicillin Blood Level (units per ml.)	Weighting	One Hour	Three Hours	Four Hours
0	0	0	0	2
0·031	1	0	0	3
0·046	1·5	0	0	1
0·062	2·0	3	1	3
0·093	2·5	0	0	0
0·125	3·0	3	2	1
0·19	3·5	2	1	1
0·25	4·0	2	1	2
0·375	4·5	3	4	1
0·50	5·0	10	4	5
0·75	5·5	1	0	2
1·0	6·0	5	2	2
1·5	6·5	4	0	1
2·0	7·0	2	3	0
2·5	7·5	1	0	0
3·0	8·0	0	0	0
4·0	9·0	1	0	0
Number of estimations		37	18	24
Arithmetic average (units per ml.)		0·81	0·68	0·37
Geometric mean (units per ml.)		0·50	0·45	0·19

penicillin, was also set up at the same time. No non-specific inhibition of the test organism was found in any of several specimens of serum taken for this purpose. The number of times a zero penicillin level was found may also be taken as a control. It must be remembered that this method is subject to relatively large inaccuracies, especially in the latter end of a series of tubes where an error of one tube means a difference of one or more units per ml.

The blood levels obtained, and their frequency distribution, are shown in table 1.

At the end of one hour and of three hours, no blood levels were below 0·062 units per ml., whereas at the end of four hours, six out of twenty-four levels were below 0·062 units, and of these two were zero readings.

The most frequent level attained at the end of the first hour was 0·5 units. There is a slight shift to lower levels at the end of three hours, and at the end of four hours this shift is very marked. In all three groups there is an occasional high blood level, which gives an unduly high result to the arithmetic mean. The actual method of assay of penicillin is one of doubling dilutions; this is in the nature of a geometrical progression, and may lead to large errors in the higher ranges. Hoffman et al. (1948) have pointed out that the geometric mean, for this reason, gives a better picture of the average blood level attained than the arithmetic mean. In the second column a linear weighting is given for each penicillin level. The arithmetic mean is found for these weightings, and the mean thus obtained is converted back into units per ml.

These results are in general agreement with those reported by other workers.

Second Series. This comprised twenty-nine cases and fifty-seven blood levels were determined. The dose given was 5,000 units per lb. birth weight in twenty-four hours.

Having shown that the very large dose of 120,000-160,000 units in twenty-four hours will give high blood levels, the attempt was made to determine whether adequate levels could be obtained with smaller doses. It was therefore decided to give 5,000 units per lb. in twenty-four hours divided into three- or four-hourly doses as required. Since in adults, 1,000 units per lb. in twenty-four hours by intramuscular injection gives adequate blood level, it might have been expected that an oral dosage of 5,000 units per lb. in twenty-four hours would give adequate blood levels in infants. The total dose per twenty-four hours was made up, and 1 ml. given either three- or four-hourly, before feeds, as in the first series. Blood was removed for estimation, one hour, three hours, and four hours afterwards as before. The results are shown in table 2.

It will be seen that compared with the higher dose the blood levels are more erratic. At the end of one hour, about one-third were below 0·062 and three-quarters of the levels were at or below 0·125 units per ml.; whereas in the first series the corresponding figures are none below 0·062, and about one-fifth at or below 0·125 units per ml. At the end of three hours in the second series about one-quarter were below 0·062 units, and over two-thirds at or below 0·125 units; whereas in the

TABLE 2

PENICILLIN LEVELS (DOSE: 5,000 UNITS PER LB. OVER TWENTY-FOUR HOURS) IN THE NEWBORN

Penicillin Blood Level (units per ml.)	Weighting	One Hour	Three Hours	Four Hours
0	0	0	1	2
0·031	1·0	5	0	3
0·046	1·5	5	2	3
0·062	2·0	4	1	1
0·093	2·5	3	2	1
0·125	3·0	5	3	1
0·19	3·5	1	0	1
0·25	4·0	0	2	3
0·375	4·5	2	1	0
0·50	5·0	4	1	0
Number of estimations		29	13	15
Arithmetic average (units per ml.)		0·154	0·161	0·097
Geometric mean (units per ml.)		0·10	0·122	0·064

first series the corresponding figures are none below 0·062, and one-sixth at or below 0·125 units.

Third Series. This series of older children comprised eight cases and sixteen blood levels were determined.

In a small series the blood penicillin levels were estimated on children between the ages of one and ten years. A dose of approximately 5,000 units per lb. in twenty-four hours was given orally ten minutes before a meal. The results are shown in table 3.

TABLE 3
PENICILLIN LEVELS (DOSE: 5,000 UNITS PER LB.) IN CHILDREN AGED 1 TO 10 YEARS

Penicillin Blood Level (units per ml.)	Weighting	One Hour	Three Hours
0	0	2	7
0·031	1·0	0	0
0·046	1·5	2	1
0·062	2·0	1	—
0·093	2·5	2	—
0·125	3·0	1	—
Number of estimations		8	8
Arithmetic average (units per ml.)		0·058	0·006
Geometric mean (units per ml.)		0·055	0·006

The blood levels in this series are appreciably lower than those obtained with the comparable dose in infants under one month.

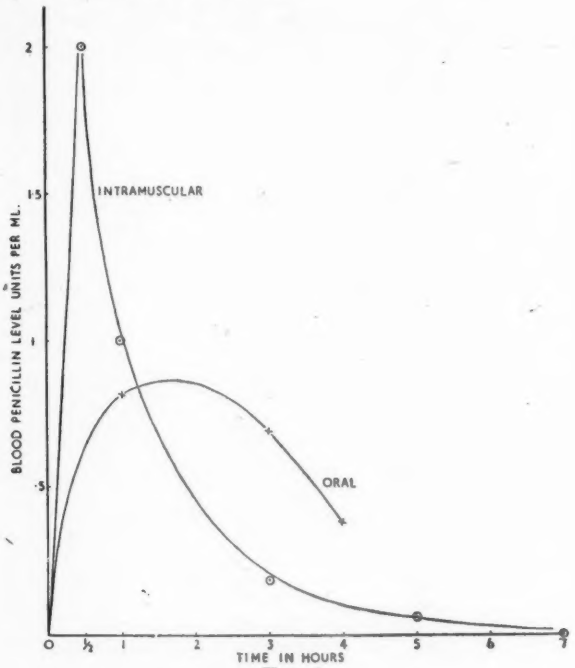

FIG. 1.

Comparison of Intramuscular and Oral Penicillin

The results indicate that 120,000 to 160,000 units in twenty-four hours in divided doses will give a very adequate bacteriostatic level in infants up to one month. A comparison between the oral administration and intramuscular injection is shown in fig. 1.

Penicillin levels following a single injection (of 20,000 units) of penicillin in a four-day-old infant weighing 7¾ lb. have been plotted. The curve for oral penicillin (20,000 units every three or four hours) is constructed from the data of table 1. The graph shows clearly that there is a higher initial level reached in the first hour after intramuscular dose, but this falls off much more rapidly than after oral penicillin, so that for the next three hours the latter levels are higher. Whether it is better to have a very high initial blood level followed by lower blood levels, or to have, as in oral penicillin, a moderately high blood level throughout the whole period, is not yet determined. It should be noted that the scatter in the blood levels after oral penicillin is such that in a proportion of cases there will be a zero blood level after four hours. This constitutes a serious argument against oral penicillin, unless this is checked by an estimation performed at the end of three or four hours, according to the intervals at which the penicillin is given.

The lower dose of 5,000 units per lb. in twenty-four hours will also frequently give a bacteriostatic level. A comparison between blood levels obtained three hours after intramuscular injection using a dose of 1,000 units per lb. in twenty-four hours and oral penicillin of five times the amount is given in table 4. The figures for blood levels after intramuscular penicillin are those given by Bodian (1946). The arithmetic and geometric means have been calculated from his results. This shows the average levels obtained are higher in this small series with oral penicillin; 18 per cent. showed zero levels with intramuscular penicillin as against 7·7 per cent.

with oral. When the levels obtained at the end of four hours after oral penicillin are included the blood levels obtained are still higher than three hours after 1,000 units given intramuscularly. It should be noted that Bodian's series refers to infants under a year, the exact age not being stated.

one 'average' and one 'low' level it was included in the low group; where one 'average' and one 'high' level were obtained, the result was included in the high group. No case had both a 'high' and a 'low' blood level. In the first series, of a total of forty-two cases, thirteen blood levels were 'low,'

TABLE 4
COMPARISON OF INTRAMUSCULAR AND ORAL PENICILLIN

Intramuscular (1,000 units per lb. in 24 hours)			Oral (5,000 units per lb. in 24 hours)			Oral (5,000 units per lb. in 24 hrs.)	
Penicillin blood level three hours after dose			Penicillin blood level three hours after dose			Penicillin blood level four hours after dose	
Units per ml.	Levels	Per cent.	Units per ml.	Levels	Per cent.	Levels	Per cent.
* 0	11	18	0·0	1	7·7	2	13·3
0·02	21	34	0·031	0	0·0	3	20·0
0·04	15	25	0·046	2	15·4	3	20·0
0·08	9	15	0·062	1	7·7	1	6·7
0·16	5	8	0·093	2	15·4	1	6·7
			0·125	3	23·0	1	6·7
			0·19	0	0·0	1	6·7
			0·25	2	15·4	3	20·0
			0·375	1	7·7	0	
			0·50	1	7·7	0	
No. of estimations	61			13		15	
Arithmetic average (units per ml.)	0·042			0·161		0·097	
Geometric mean (units per ml.)	0·032			0·122		0·064	

* Bodian, 1946.

Factors Influencing Blood Levels

It has been generally accepted that oral penicillin in infants gives higher blood levels than comparable amounts in older children. The results obtained in this investigation support this. Henderson and McAdam (1946) point out that whereas in adults it is necessary to give orally five times the intramuscular dose in order to obtain comparable blood levels, in infants an oral dose of 10,000 units will give a bacteriostatic level for a longer time than the same dose given intramuscularly although a higher initial dose is reached with the latter. A similar result is shown in fig. 1 where an oral dose of 20,000 units is compared with the same amount given intramuscularly. Again, an oral dose of 5,000 units per lb. in twenty-four hours gives better levels than 1,000 units per lb. in twenty-four hours given intramuscularly.

Various reasons have been advanced to account for this discrepancy between infants and older children. In an attempt to determine whether our results would throw any further light on the problem of factors influencing blood levels, we divided our cases into those showing 'high', 'average', and 'low' blood levels. The division was purely arbitrary and is shown in fig. 2. Where a case had fifteen were 'average,' and fourteen were 'high.' In the second series of a total of twenty-nine cases, twelve blood levels were 'low,' nine were 'average', and eight were 'high.'

The results were then analysed for the clinical factors of age (table 5), fluid intake, prematurity, and dosage to see if there were any significant and constant differences between the three groups.

In infants under forty-eight hours most give high penicillin blood levels; in the infants under seven days there is a slight preponderance in the high level group; in infants between eight and fourteen days there is a much greater preponderance in the low level group. The number of infants over fourteen days old is small but results indicate an approximately equal distribution in all three groups.

The fluid intake was ascertained on the same day that the penicillin was started and the day before the penicillin level was estimated. Table 6 shows the number of results falling into each group.

Of the infants eight days of age or over, five had a fluid intake of less than 2 oz. per lb. birth weight in twenty-four hours, while twenty-seven had a fluid intake of 2 oz. or over (see table 6a).

These results show a tendency for low fluid intake to be associated with high blood levels and vice versa.

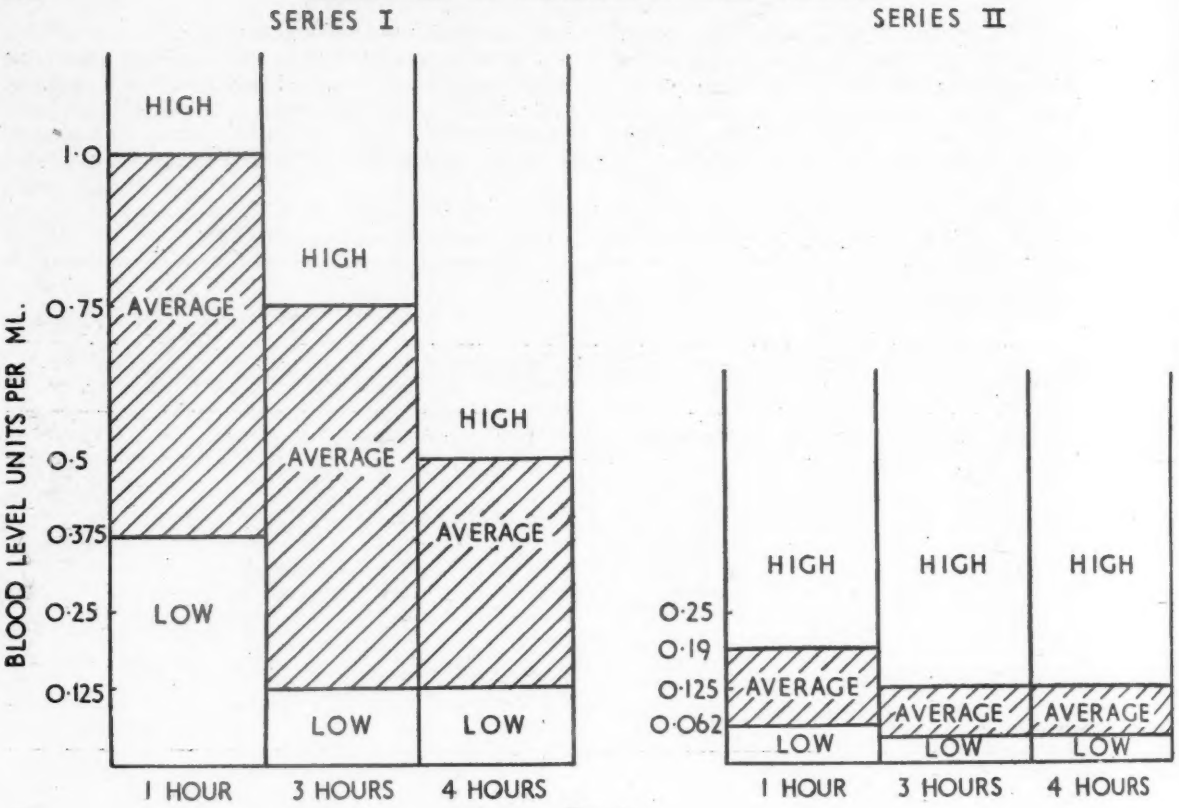

FIG. 2.
Penicillin blood levels: division into high, average and low groups

TABLE 5
RELATION OF AGE TO PENICILLIN BLOOD LEVELS IN THE NEWBORN

Age (When penicillin level was estimated)	Penicillin Blood Level Group		
	High (No. of cases)	Average (No. of cases)	Low (No. of cases)
48 hours or less	7	1	1
0-7 days (including first group)	15	14	10
8-14 days	3	8	12
Over 14 days	4	2	3

TABLE 6
RELATION OF FLUID INTAKE TO PENICILLIN BLOOD LEVEL

Fluid Intake	Penicillin Blood Level Group				
	High (No. of cases)	Average (No. of cases)	Low (No. of cases)	Mean Age (in days)	Range (in days)
Less than 1 oz. per lb. in 24 hours	8	2	0	1·6	1–2
1-2 oz. per lb. in 24 hours ..	8	6	7	5·0	1–16
Over 2 oz. per lb. in 24 hours	6	16	18	18·0	5–30

TABLE 6a

FLUID INTAKE AND PENICILLIN LEVEL IN INFANTS OVER 7 DAYS OLD

Fluid Intake	Penicillin Blood Level		
	High	Average	Low
Intake under 2 oz. per lb.	3	1	1
Intake 2 oz. per lb. or over	4	10	13

In table 7 is shown the relation of prematurity to blood levels. Although the number of premature infants included was small there was a slight preponderance of results in the high level group. This was true in both series, and did not seem to be due to high dosage per lb. Amongst full-term infants the numbers in all three groups were approximately the same.

TABLE 7

RELATION OF PREMATURITY TO PENICILLIN BLOOD LEVEL

	Penicillin Blood Level		
	High	Average	Low
Premature infants ..	5	7	2
Full term infants	17	17	23

In the first series the dose per lb. per twenty-four hours varied between 13,000 and 40,000 units (see table 8).

The low levels encountered with doses of 20,000 units per lb. in twenty-four hours occurred in infants of eight days or over and with a fluid intake of 2 oz. per lb. birth weight in twenty-four hours or more.

Other factors considered included the simultaneous use of sulphonamides, the previous use of intramuscular penicillin, and the presence of gastro-intestinal upsets. There was no evidence in our series that any of them had any effect on the blood levels. In six cases where intramuscular penicillin had previously been given it had been stopped at least thirty-six hours before the oral blood level was estimated. There were no gastro-intestinal upsets. Oedema was present in only three infants. Of these, two had high blood levels and one average. Jaundice was described as deeper than normal in two cases, both with ' high ' levels.

Variation with Age in Penicillin Blood Levels

In discussing the variation of penicillin blood levels with age two chief points of interest arise: (1) Why are better and more consistent blood levels attained with oral penicillin in infants than in adults, and (2) at what age do the results become less satisfactory. Husson (1947) in recording the blood levels following the administration of oral penicillin to infants between the ages of one week and five months, has discussed some possible reasons for the higher blood levels in infants compared with older children and adults. The second point was not investigated, as our cases are confined to the neonatal period. As for the first point, the following reasons have been postulated. (1) The lower gastric acidity in infants might mean that less penicillin was destroyed. We have done no gastric analyses, but our results show a definite tendency for blood levels to be higher in the first week of life than later; according to Miller (1941), gastric acidity in infants is high on the first day, falls to a low level on the eighth to tenth day, and slowly rises thereafter. In our series, therefore, higher blood levels are obtained when gastric acidity is high; this is the reverse of the expected effect. This point is of increased interest because penicillin tablets for oral use containing sodium citrate are now being marketed; we have, since this series of cases was collected, seen infants who develop oedema while on such ' citrated ' tablets, and feel that such ' buffering ' may prove troublesome as well as apparently unnecessary.

TABLE 8

RELATION OF DOSE PER LB. BIRTH WEIGHT IN TWENTY-FOUR HOURS AND BLOOD LEVELS (SERIES I)

Dose per lb. per 24 hours	Penicillin Blood Level Group		
	High	Average	Low
Below 15,000	2	2	2
15–under 20,000	3	5	6
20–under 25,000	5	4	3
25–under 30,000	2	2	2
30,000 or over	2	2	0

Duodenal absorption may be more rapid and effective in infants. We have no evidence on this point.

Penicillinase-producing organisms in the intestine are probably less frequent in the first day or two of life. Our series does suggest that in the very early days of life (i.e. during the first forty-eight hours) when the large intestine is relatively sterile, higher blood levels are attained. The question of age in our series, however, is very closely correlated with a low fluid intake, as shown in table 6. Variation in fluid intake might account for the differences between infants under forty-eight hours and those after the first week, but obviously could not account for the differences between infants and older children (tables 2 and 4).

Poor renal function in infants with consequent diminished excretion has been suggested as a possible factor. The level of penicillin in the blood after intramuscular injection appears to be reduced as rapidly by renal excretion in the infant as it is in the adult; in other words, the blood level curve obtained is essentially similar. This suggests that renal function is not an important factor. It is interesting to note that in our series there seemed to be little or no relation between oedema and blood level variation.

Liver function has not to our knowledge been shown to bear any relation to penicillin blood levels in infants or adults, but this point might be worth investigating further in the newborn.

On our small series, therefore, we consider that one important factor causing differences in penicillin blood level during the neonatal period is fluid intake. Increased absorption from the intestine, possibly due to the relative absence of penicillinase-producing organisms in the first month of life, may account for higher blood levels in the newborn compared with older children and adults.

Indications for Treatment

The cases treated fell into three main groups, (1) skin sepsis of varying degrees of severity, (2) upper respiratory infection including otitis media, and, (3) prophylactic treatment for atelectasis. There was no definite correlation between the rate of healing of lesions and the penicillin blood level, but it should be noted that no cases of severe generalized infection were treated by this method. Treatment with oral penicillin was found satisfactory for the rather limited sphere in which it was used.

No definite toxic effects were observed. Only one baby vomited whilst on penicillin, and he had been vomiting slightly before treatment was started. One infant developed a rash, but he was also on sulphadiazine and the rash cleared on stopping the latter. It may be mentioned that the nursing staff

TABLE 9

COMPARISON OF SULPHATHIAZOLE PASTE AND ORAL PENICILLIN FOR SKIN LESIONS

Results	Sulphathiazole Paste	Per cent.	Oral Penicillin	Per cent.
No. of cases treated	48		48	
Healed in four days or less	31	64·6	36	75
Healed in more than four days	9	18·8	10	20·8
Failed	8	16·6	2	4·2

TABLE 10

BACTERIOLOGY OF SKIN LESIONS

	Sulphathiazole Paste	Oral Penicillin
No. of cases	48	48
Cultures	30	28
Coagulase positive Staph. aureus	26	26
Coagulase positive Staph. aureus and diphtheroids	1	0
Coagulase positive Staph. aureus and non-haemolytic streptococcus	1	0
Organisms sensitive to both penicillin and sulphathiazole	12	14
Sensitive to penicillin only	3	0
Sensitive to sulphathiazole only	3	2
Not sensitive to either	0	1

have an impression that some infants take their feed less satisfactorily when on penicillin. The drug should not be used in the presence of diarrhoea or vomiting and we would not ourselves use it in very acutely ill infants, as it may be possible that absorption is less good in such cases.

Although 5,000 units per lb. in twenty-four hours gave adequate levels in a majority of cases, there is a sufficiently wide scatter to make one chary of advising this as a routine dose. In infants under a week old, in our series, occasional low levels were encountered unless a dose as high as 20,000 units per lb. in twenty-four hours was used, while in infants over a week, there were sometimes low levels below 30,000 units per lb. We would suggest, therefore, that a dose of at least 20,000 units per lb. in twenty-four hours, given before feeds, should be used as a routine.

Comparison of Sulphathiazole Paste and Oral Penicillin

The types of skin lesions treated were paronychia, boils, pustules, and mildly infected forceps wounds. A total of ninety-six cases were treated, divided equally into those treated with penicillin and sulphathiazole paste (5 per cent.) respectively. Cases of intertrigo or sore buttocks which were not infected were not included. These cases were chosen in the following way. All infants developing skin infection in alternate wards (housed in separate blocks) were treated routinely either with sulphathiazole paste or oral penicillin. (See table 9.)

A culture was possible in a total of fifty-eight cases, from which a pure growth of coagulase positive Staph. aureus was obtained in fifty-two cases; in two further cases either diphtheroids or non-haemolytic streptococcus were isolated in addition to Staph. aureus. In four instances, coagulase negative Staph. albus only was isolated. The sensitivity to penicillin and sulphathiazole was determined in thirty-five instances. The results obtained are given in table 10.

The results show a slight superiority in favour of penicillin. Though the difference is small, and might be attributed to chance, an impression has been gathered from experience with both forms of treatment that although sulphathiazole paste is adequate for cases where there are only a few pustules, where lesions are numerous this treatment is unsatisfactory.

Summary

1. The blood levels following (a) a high dose of 20,000 units penicillin three- or four-hourly, (b) the lower dose of 5,000 units per lb. in twenty-four hours have been ascertained in a group of infants under one month of age.

2. It is shown that, whilst the lower dose frequently gives an adequate bacteriostatic level, the higher dose is preferable since an adequate level is reached in almost all cases.

3. We would suggest a routine dose of 20,000 units per lb. in twenty-four hours.

4. The factors influencing the higher blood levels in infants as against older children are discussed. It has been shown that higher blood levels are associated with decreased fluid intake, and that the younger the infant, the higher, in general, the blood level. No completely acceptable explanation of the difference has been found, but it is thought that either better absorption from the small intestine, or less destruction in the colon may be a much greater factor than has been supposed.

5. In minor skin lesions in infants penicillin orally appears slightly superior to sulphathiazole paste applied locally.

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UREA CLEARANCE IN THE IMMEDIATE POST-NATAL PERIOD

BY

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In the growing volume of literature concerning renal function in the newborn infant there is as yet little mention of urea clearance in the immediate post-natal period: that is in the first three or four days of life. Barnett (1940) made observations on inulin clearance in infants of five to nine days old. The investigations of McCance and Young (1941) were made on infants of seven to fourteen days old. They also made observations on three infants aged six to thirteen days: these infants had meningocoeles. Experimental studies were made by Barnett, Perley, and McGinnis (1942) on a twenty-four hour old infant who had an extroversion of the urinary bladder. The conditions of the experiment were abnormal. The work of Gordon, Harrison, and McNamara (1942) deals with full-term infants of eight to sixty-five days and premature infants of seven to seventy-three days old. Dean and McCance (1947) have carried out some most interesting experimental studies on infants of two, three, and four days old. In these instances, the infants suffered from inoperable meningomyelocoeles. They were studied under conditions which do not normally pertain at this age period.

The observations now recorded were made on healthy spontaneously delivered full-term male and female infants. In each case the mother had a normal pregnancy and puerperium. No clinical abnormality was detected in these infants during their stay in hospital. The infants are divided into three groups each of which, with the method used and the data obtained, are described seriatim. The groups are referred to as groups I, II, and III.

Method

Group I. This group comprised nine male infants. The details of age and weight at the time of the commencement of the observation period are given in table 1. The surface area, calculated according to the recommendations of Howland and Dana (1913), and the factor required for correction to an adult standard of 1·73 sq. m. are given in the same table. The duration of the observation period is given in each case. Five of the infants were observed for two periods, making a total of fourteen observation periods, during which forty-one specimens of urine were collected.

These specimens of urine were obtained by using an apparatus previously described (Thomson, 1944). The apparatus gives accurate timing and avoids the need for continual observation. In order to present a non-wettable surface to the urine, a coating of hard paraffin is used as far as possible. Even so, a small quantity of urine is lost in wetting surfaces. Experimental observation has shown this quantity to be approximately 0·3 ml. This amount has, therefore, been added to the measured volume of each specimen of urine and the resulting volume is considered to be the true volume of urine passed. It is the figure used for all calculations.

The apparatus was fixed in position about 9 a.m., and, after the first passage of urine had been timed and recorded, specimens of urine were collected. They were preserved under toluol and were analysed in the biochemistry laboratory of the Royal Infirmary, Edinburgh, as soon afterwards as possible. The method of Van Slyke was used for the estimation of urea.

The specimens of blood were obtained by heel stab and were taken during the observation period. The time at which they were taken is given in table 1. In one instance, owing to the long duration of the observation period, two specimens were taken. These specimens were analysed in the biochemistry laboratory of the Royal Hospital for Sick Children, Edinburgh. Nessler's reagent was used to determine the ammonia liberated by urease and the results read by electro-photometer.

RESULTS. The mean volume of the individual specimens of urine was 12·25 ml. and the standard deviation 8·12 ml. The mean minute volume was 0·0682 ml. and the standard deviation 0·0650 ml. The standard deviations are expressive of the great range of the total and the minute volumes. These figures are in conformity with those published showing the average daily volume of the urine, and the average volume of urine passed at each voiding, in the first five days of life (Thomson, 1944).

The mean blood urea nitrogen was 19 mg. per 100 ml., with a standard deviation of 7·00 mg. This compares favourably with the published work of Lucas et al. (1921), Schultz and Pettibone (1915), and Sedgwick and Ziegler (1920).

The urea clearances which have been calculated

TABLE 1

DATA OF GROUP I INFANTS

Case no.	Age at commencement of observations (hours)	Weight (g.)	Surface area (sq. m.)	Correction factor (1·73/surface area in sq. m.)	Total duration of observation period (hours)	Time at which blood was taken after commencement of observations (hours)	Number of urine specimens	Blood urea nitrogen (mg. per 100 ml.)
1a	15·6	3,345	0·2346	7·37	22·25	7·66	4	23
1b	41·8	3,289	0·2318	7·46	8·58	6·25	2	23
2	104·7	3,289	0·2318	7·46	52·11	10·83	4	27
						47·00		19
3	34·2	3,515	0·2428	7·10	16·16	10·25	2	15
4a	23·0	3,232	0·2296	7·53	8·16	5·08	3	16
4b	51·0	3,090	0·2222	7·80	6·10	2·00	3	16
5a	53·4	2,523	0·1949	8·88	4·20	1·83	3	14
5b	123·5	2,523	0·1949	8·88	8·00	1·50	4	14
6a	31·1	2,892	0·2127	8·13	3·42	3·50	1	16
6b	102·3	2,807	0·2084	8·30	6·00	2·58	3	15
7	45·1	3,969	0·2647	6·54	11·05	9·58	2	16
8	50·1	3,232	0·2296	7·53	10·83	4·58	3	23
9a	19·3	3,402	0·2373	7·29	9·83	5·33	3	25
9b	29·1	3,260	0·2305	7·50	21·33	17·00	4	24
Totals					188·02		41	
Mean	51·75				13·43	7·58		19

are shown in fig. 1 where they are plotted against the minute volumes of the urine. Clearances calculated from data obtained during the same observation period have been joined by straight lines. Averages can be struck by raising perpendiculars at selected urine minute volumes to cut these lines. Readings are taken at the point of intersection. The general trend of the figure shows that the volume of blood cleared tends to increase with an increase in the minute volume of the urine. There are three exceptions. The mean volume of blood cleared of urea is 1·0009 ml. per minute equal to 0·19 mg. urea nitrogen.

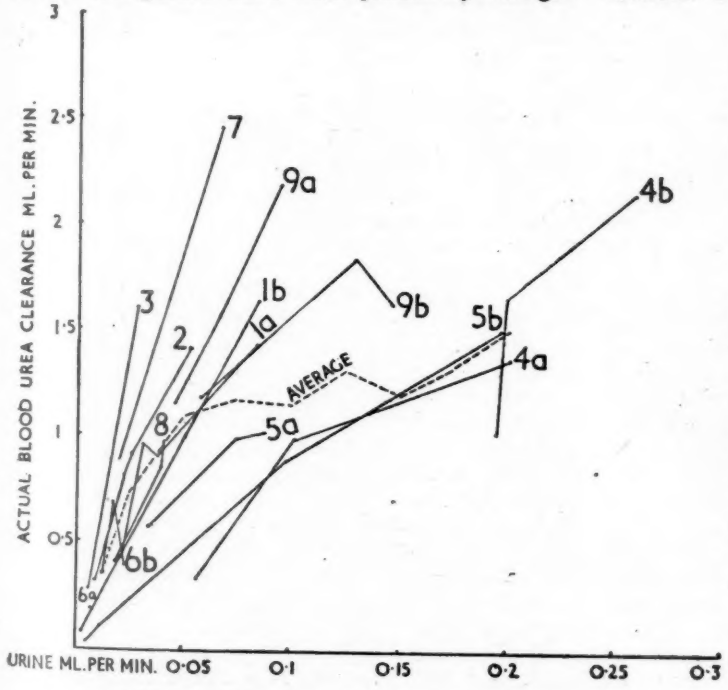

FIG. 1.—Group 1: individual urea clearances.

Group II. This group comprised thirteen male infants. In table 2 the same details are given as in the case of the infants in group I. In addition the factor for correction for an adult standard of 70 kg. body weight is given. Eight of the infants were observed for two periods making a total of twenty-one observation periods during which sixty specimens of urine were obtained. At the commencement of fifteen of the observation periods the infant was given by gavage 3 g. of urea dissolved in 30 ml. of water prior to the fastening on of the apparatus for collecting urine. The infant was not upset by this procedure. When regurgitation did occur, it was infrequent and the amount was small. The remaining six observation periods were in the case of infants who had already been observed and had been given urea approximately twenty-two

TABLE 2
DATA OF GROUP II INFANTS

Case no.	Age at commencement of observations (hours)	Weight (g.)	Correction factor (70 kg./body weight)	Surface area (sq. m.)	Correction factor (1·73/surface area in sq. m.)	Total duration of observation period (hours)	Time at which blood was taken after giving urea (hours)	Number of urine specimens	Blood urea nitrogen (mg. per 100 ml.)
10a	35·5	3,771	18·56	0·2551	6·8	8·40	6·40	3	33
10b	132·7	3,686	18·99	0·2510	6·9	4·25	1·10	5	42
11a	31·7	3,232	21·66	0·2296	7·53	6·95	7·00	1	41
11b	97·3	3,118	22·45	0·2236	7·7	14·01	14·00	2	33
12a	23·3	3,771	18·56	0·2551	6·8	9·68	5·35	2	27
12b	46·2	3,629	19·29	0·2483	6·97	11·20	28·06*	3	18
13	21·1	3,005	23·29	0·2182	7·9	11·17	2·40	4	50
							12·33		36
14	35·7	2,722	25·72	0·2044	8·4	9·08	2·00	3	33
15a	52·8	3,657	19·14	0·2496	6·93	12·25	4·00	3	57
15b	78·2	3,515	19·91	0·2428	7·1	13·60	34·83*	2	22
16	82·6	3,572	19·60	0·2455	7·05	8·33	2·25	3	28
17a	61·1	3,317	21·10	0·2332	7·42	12·38	6·50	2	40
17b	80·1	3,289	21·29	0·2318	7·46	12·92	33·50*	1	26
18a	20·5	4,706	14·87	0·3003	5·76	5·08	3·10	3	40
18b	42·8	4,649	15·06	0·2975	5·81	15·33	25·43*	3	28
19a	15·1	3,912	17·89	0·2619	6·6	9·97	4·33	3	33
19b	33·5	3,714	18·85	0·2524	6·85	5·41	19·90*	4	21
20a	13·6	3,317	21·10	0·2332	7·42	13·00	7·66	4	31
20b	39·1	3,147	22·24	0·2253	7·68	16·75	34·60*	3	16
21	25·0	2,863	24·45	0·2113	8·19	3·17	1·25	3	44
22	22·2	3,714	18·85	0·2524	6·85	10·83	1·33	3	50
Totals						213·76		60	
Mean	47·15					10·79			34

* Urea not given at commencement of second observation period.

hours previously (see table 2). No other change in method was made. Apart from the blood urea nitrogen the differences between the means of the various data in tables 1 and 2 are not statistically significant.

RESULTS. The mean volume of the individual specimens of urine was 14·8 ml. and the mean minute volume was 0·0892 ml. These figures are not significantly different from the corresponding figures of group I. The mean blood urea nitrogen was 34 mg. per 100 ml. with a standard deviation of 10·63 mg. This is 1·8 times the corresponding figure for group I. The difference between the two figures may be taken as an expression of the amount of urea absorbed following gavage. The urea clearances which have been calculated are shown in fig. 2 where they are plotted against the urine minute volumes. As in fig. 1 clearances calculated from data obtained during the same observation period have been joined by straight lines, and averages obtained by the same method as in group I. The mean volume of blood cleared of urea is 2·008 ml. per minute, equal to 0·68 mg. urea nitrogen.

Group III. In this group there are sixteen female infants, one of whom was observed on two occasions, making a total of seventeen observation periods. In table 3 details concerning the infants are given as in the case of groups I and II.

The infants were allowed to breast feed at 6 a.m. and given no further food or water until the end of the observation period. At 9 a.m. the urinary bladder was emptied by catheter and the infant immediately given 3 g. urea in 30 ml. water by gavage. The infants were not restrained. Thinking it unlikely that urine would be passed spontaneously within an hour, the urine collecting apparatus was not used. Unfortunately this resulted in the loss of one or two specimens. The infants were catheterized at 10 a.m., 11 a.m., and 12 noon and the urinary bladder emptied. Catheterization was not always successful for sometimes urine leaked past the side of the catheter. The volumes of the thirty-four complete individual specimens which were obtained are given in table 3.

To make sure that the blood urea concentration was raised within an hour, specimens of blood were taken by heel stab from nine of the infants at 9 a.m.

before giving the urea. At 10 a.m. blood was taken from all the infants: at 11 a.m. blood was taken from four infants. The blood urea concentration of all these specimens is given in table 3.

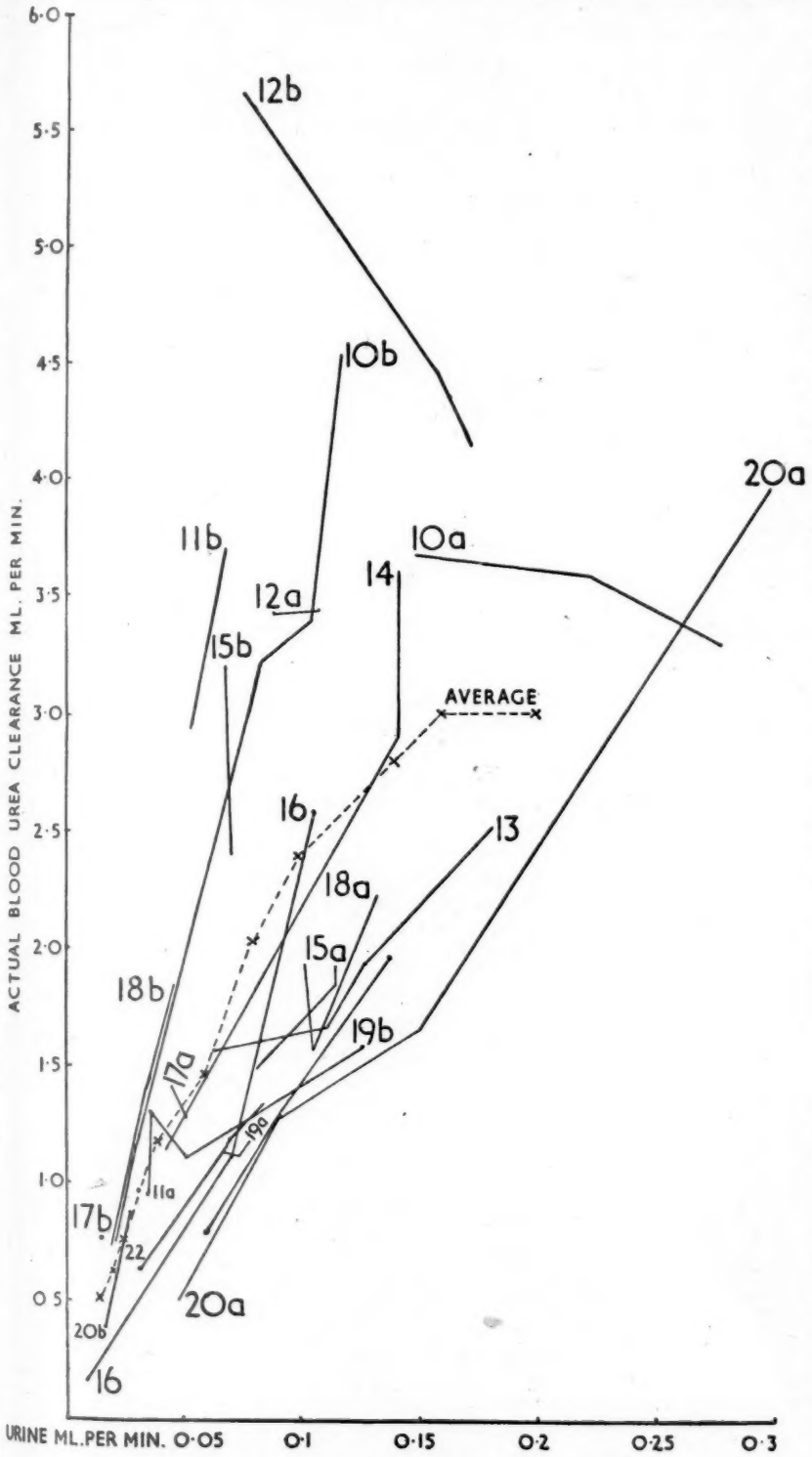

FIG. 2.—Group II: individual urea clearances.

RESULTS. The average of the individual urine minute volumes was 0·0705 ml. The difference of this figure from the corresponding figure of 0·0682 ml. for group I and 0·0892 ml. for group II is not statistically significant.

The mean blood urea nitrogen at 10 a.m. was 43 mg. per 100 ml.

The urea clearances which have been calculated are shown in fig. 3 where they are plotted against the urine minute volumes. As in figs. 1 and 2 clearances calculated from data obtained during the same observation period have been joined by straight lines, and from these averages have been estimated. The mean volume of blood cleared of urea is 1·5514 ml. per minute, equal to 0·6665 mg. urea nitrogen.

Fig. 4 shows the urea concentration of the individual urine specimens plotted against the time at which they were taken. Specimens from the same infant are joined by straight lines. It is shown that with one exception, a day-old infant, there is always an increase in the concentration of urea. In the one exception it will be noted that the urine urea concentration at 9 a.m. was at a higher level than that found in any of the other infants in the group.

Discussion

The results now recorded may be looked upon as complementary to those of McCance and Young (1941). It is important to note that their observations were made on infants who were in their second week of life, for at this age the fluid intake of the infant who is solely breast fed is more than five times the intake of an entirely breast fed two-day-old infant and about three times that of a three-day-old infant (Thomson, 1944).

The infants of group I of this series of observations

TABLE 3

DATA OF GROUP III INFANTS

Case no.	Age at commencement of observations (hours)	Weight (g.)	Correction factor (70 kg./body weight)	Surface area (sq. m.)	Correction factor (1·73/surface area in sq. m.)	Blood urea nitrogen per 100 ml.			Number and volume of urine specimens				
						9 a.m.	10 a.m.	11 a.m.	9 a.m. (ml.)	10 a.m. (ml.)	11 a.m. (ml.)	12 noon (ml.)	1 p.m. (ml.)
23	75·3	3,345	20·92	0·2346	7·37	24	47	—	+	6·8	4·2	3·5	N.C.*
24	118·2	2,835	24·69	0·2099	8·20	21	57	—	+	5·6	7·4	part	N.C.
25	38·8	2,948	23·74	0·2154	8·00	—	38	—	+	part	part	Nil	N.C.
26a	131·5	3,005	23·29	0·2181	7·90	—	33	33	Nil	5·9	Nil	Nil	N.C.
26b	203·5	3,090	22·65	0·2222	7·80	—	33	—	+	5·0	6·6	part	N.C.
27	146·1	4,167	16·82	0·2743	6·30	14	48	—	+	6·4	part	4·1	N.C.
28	44·4	3,374	20·75	0·2359	7·33	28	47	45	+	1·9	1·7	1·1	0·6
29	53·2	2,948	23·74	0·2154	8·00	21	44	—	+	1·6	3·9	4·0	N.C.
30	63·3	3,515	19·91	0·2428	7·10	22	48	—	+	5·3	6·0	3·6	N.C.
31	106·0	2,722	25·72	0·2044	8·50	9	36	—	+	part	part	3·0	N.C.
32	132·9	3,090	22·65	0·2222	7·80	—	52	—	+	5·3	part	5·8	N.C.
33	127·5	2,438	28·71	0·1908	9·10	—	34	—	+	Nil	2·5	N.C.	N.C.
34	121·1	3,090	22·65	0·2222	7·80	—	33	—	+	3·6	Nil	part	N.C.
35	153·1	2,693	25·99	0·2031	8·50	12	43	—	Nil	4·7	3·4	part	N.C.
36	39·3	3,685	18·99	0·2510	6·90	22	68	—	+	3·1	1·8	Nil	N.C.
37	126·7	2,551	27·43	0·1962	8·80	—	38	40	+	6·1	4·2	5·3	N.C.
38	212·8	2,608	26·84	0·1990	8·70	—	35	36	+	4·6	5·5	N.C.	N.C.
Mean	111·58					19	43				4·238 ml.		

* N.C. = not catheterized.

received no fluid other than that which they could obtain at the breast. Because of this the minute volumes obtained are less than those recorded by McCance and Young. They recorded minute volumes of the order of 0·1 to 0·15 ml. per minute which compares with a mean of 0·0682 ml. for this group of observations. The blood urea concentrations recorded by McCance and Young were lower, the average being 16·4 mg. urea per 100 ml. (7·66 mg. urea nitrogen per 100 ml.) compared with a mean of 19 mg. urea nitrogen per 100 ml. in this series. This difference in the two age periods is in conformity with the findings of Sedgwick and Ziegler (1920).

Despite these differences comparison may be made if the data are 'corrected' to an agreed standard. If the agreed standard be an adult standard, comparison may be made with it at the same time. The ratio between the body surface area, body weight, kidney weight, and the metabolic rate of the infant, and the corresponding data for an ideal theoretical adult have been suggested as correcting factors which might be used. McCance and Young (1941) have investigated the application of these various factors and on the data before them show that the body surface area factor is the most reasonable one to use.

After correcting each observation in group I to a standard of 1·73 sq. m. body surface the observations were plotted after the manner of fig. 1 and averages were struck. These averages in the form of a graph are given in fig. 5. In the same figure there is given for comparison the graph for a theoretical adult having a surface area of 1·73 sq. m. and a body weight of 70 kg. The graph presented by McCance and Young (1941) representing the similarly corrected observations of their series is also given.

Comparison of these three graphs shows that judged by this standard the power of the kidney to clear urea from the blood in the immediate post natal period is far below that of the adult kidney and is also less than that of the two-week-old infant. In addition, the form of the graph representing the present observations differs from that representing the infant in the second week of life. The change in the form of the graph representing the observations of group 1 is sufficiently marked and abrupt to require some explanation.

Consideration of fig. 1 shows that the change in the form of the graph occurs at about a urine minute volume of 0·05 ml., that is, less than the mean minute volume. Also the impression is obtained that the scatter of the individual observations above 0·05 ml. per minute is much wider than the scatter at lower minute volumes. This impression is confirmed by the coefficient of correlation between the blood urea clearance and the urine minute volume which for the observations below 0·05 ml. urine per minute is +0·657 while for those above 0·05 ml. urine per minute it is +0·130.

In a search for an explanation the following points may be considered. (1) The graph may represent all the kidney is required to do by way of

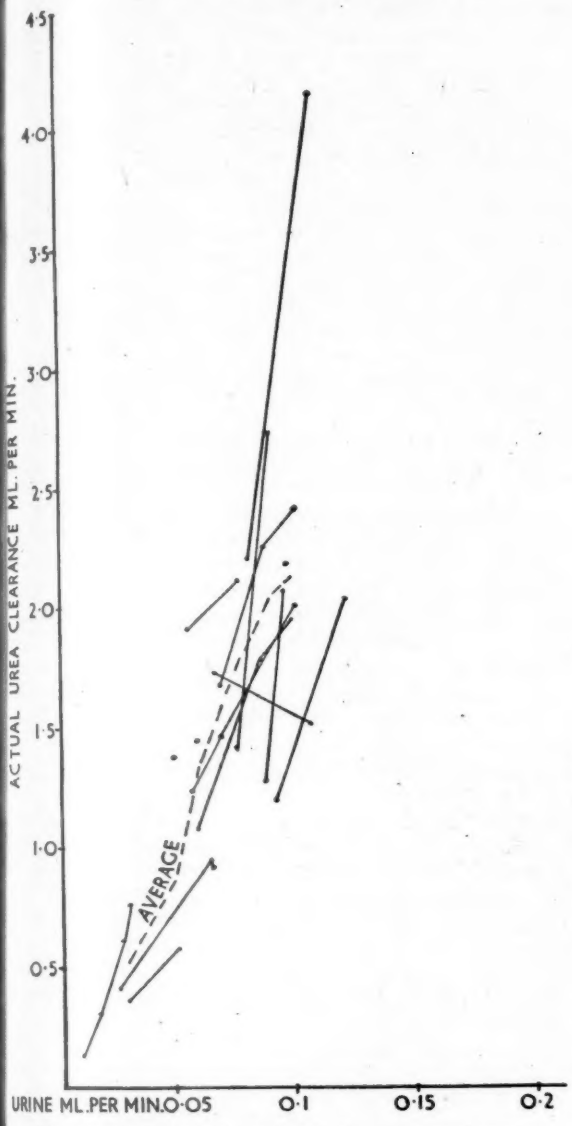

FIG. 3.—Group III: individual urea clearances.

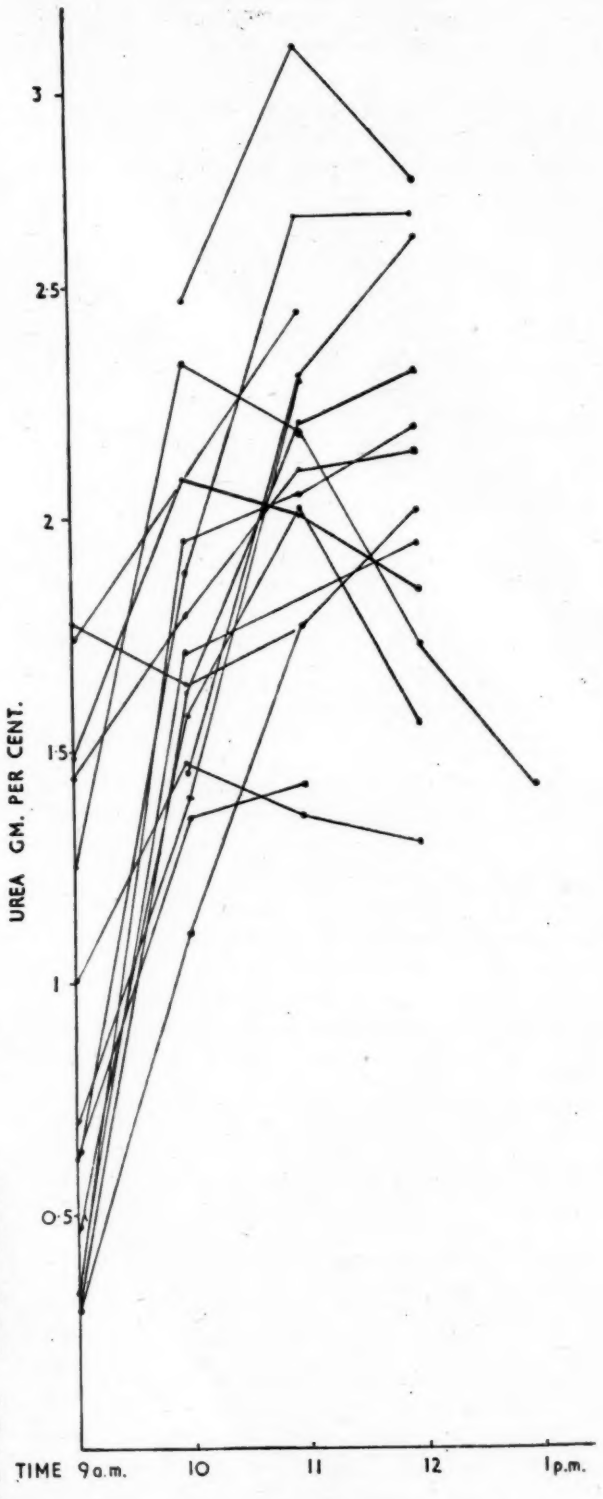

FIG. 4.—Group III: concentration of urea in urine.

urea clearance in the immediate post-natal period, and this may not be the same as the maximum clearing power; (2) in those observations showing urine minute volumes over 0·05 ml. per minute, the rate of flow through the tubules may have been too fast to permit of adequate concentration; (3) the possible effect upon the data of the failure of the infant to empty the bladder when voiding urine spontaneously.

The data obtained from group II gives some information on the first two of these points. The graph representing the averages of these observations shows little change in its form and is more like a straight line, fig. 2. The urea fed to this group of infants has not produced a diuresis and

the difference between the urine minute volumes of groups I and II is not statistically significant. The group II observations corrected for surface area have been averaged in the same manner as the observations of group I, and are given as a graph in fig. 5. At urine minute volumes up to 0·4 ml. corrected the graphs for groups I and II virtually coincide. Above this point they diverge. It seems reasonable to infer from this that the urea clearances in groups I and II up to a urine minute volume of 0·05 ml. per minute are of the nature of maximum urea clearances and at urine minute volumes over this figure the maximum urea clearance rate is maintained by group II and not by group I. The group II observations also show that at urine minute volumes over 0·05 ml. the flow through the tubules is not too fast to permit of tubular resorption.

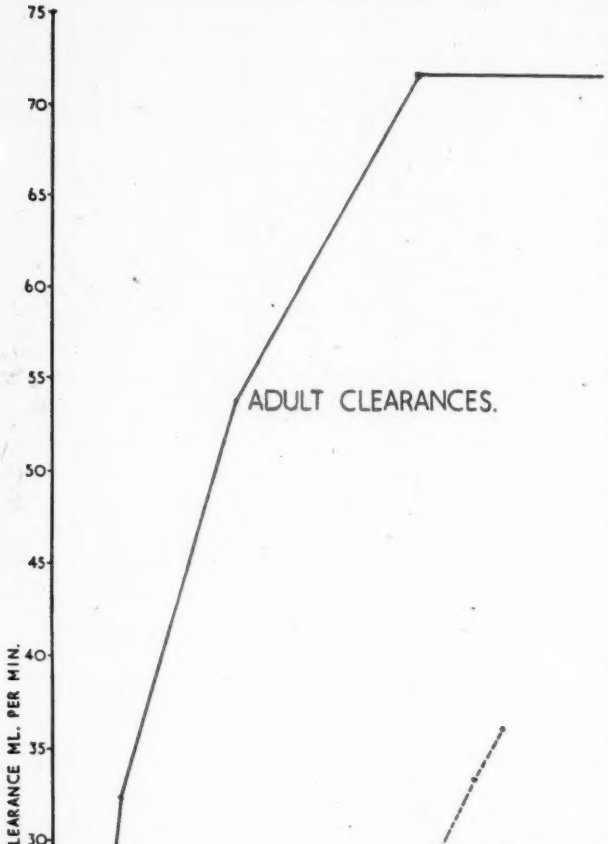

FIG. 5.—Comparison of infant and adult clearances on a basis of body surface area of 1·73 sq. m.

It will be observed that in calculating the clearances for group II it has been assumed that the blood urea nitrogen level remains constant throughout the observation period. Since it may well be doubted whether this is so, the blood urea nitrogen level was investigated several times in two infants. Fig. 6 shows the results obtained over a period of some forty-eight hours. In the same figure the blood urea nitrogen concentrations for all the infants in group II are given. In the case of the six infants who were not given urea at the commencement of the second observation period the blood urea nitrogen concentrations for the first and second periods have been joined by straight lines. The trend of these lines shows a certain resemblance to the graphs obtained from the two infants, A and B, whose blood urea nitrogen concentrations were observed more frequently. There is little doubt that the blood urea nitrogen concentration remains at a high level initially and that it does so for periods comparable with the mean average duration of the observation period. Unfortunately the high concentrations are not necessarily stable, so that the data obtained in respect of group II are not free from objection. Moreover, the possible effect upon the data of the failure of an infant to empty the bladder is not considered in this group.

In group III, by shortening the period of observation to an average of two hours per infant and emptying the bladder by catheter at hourly intervals, one removes as far as possible the objection that the bladder may not be emptied at the time of voiding urine. One also mitigates in very large measure the objection that the blood urea nitrogen may not remain at a stable level during the observation period. This is shown by a comparison of the four blood urea nitrogen levels at 11 a.m. with those taken at 10 a.m. from the same infant (table 3).

On five occasions no urine was obtained on catheterizing, and no evidence could be found to show that the infant had voided urine spontaneously before being catheterized. Because of this it may be questioned whether the kidney secretes urine continuously. Be that as it may, the fact that there is no statistical significance in the differences between the urine minute volumes of the three groups suggests that from this point of view, at

least, the observations of the three groups are comparable.

In group III as in group II urea did not produce a diuresis. The graph representing the averages of the observations in group III resembles the graph for group II in as much as it is almost a straight line (fig. 3).

The observations obtained from group III after individual correction for surface area, have been averaged in the same manner as the observations for groups I and II. This is shown in fig. 5. It is apparent from this representation that there is a great similarity between the averages of the observations for groups II and III so that the inference already drawn from a comparison of the graph representing groups I and II appears to be confirmed. The inference was that normally in the immediate post-natal period at urine minute volumes of 0·05 ml. or less (corrected 0·4 ml.) the urea clearance may be considered to be a maximum one, but that at urine minute volumes over this figure it is less than maximum.

In fig. 5 a comparison may also be made between the averages for groups II and III and the averages of the observations of McCance and Young. It is shown that the urea clearance in relation to the urine minute volume for groups II and III is greater than that which normally obtained in the second week of life. This observation suggests that the data of McCance and Young do not reflect the maximum clearing power of the kidney but rather a normal urea clearance for the age period. In the same figure (no. 5) comparison of groups II and III may also be made with the urea clearance of a standard adult of 1·73 sq. m. body surface area. On this basis the urea clearances for groups II and III, though better than group I, shows that the kidney in the immediate post-natal period is less efficient than the adult kidney.

In their work on urea clearance McCance and Young showed that a basis of body weight was the only basis to which their observations could be corrected in order to reach a urea clearance comparable with that of an adult. They rejected this basis because of the very high urine minute volume which it entailed (fig. 7.) In view of the greater renal efficiency shown by groups II and III it was thought desirable to make a comparison between their urea clearances and those of a standard adult on a weight basis. After individual correction of the observations in each of groups II and III, averages were struck and graphs obtained. These graphs are shown in fig. 7. It is apparent that on this basis also an adult level of urea clearance has not been reached at any urine minute volume.

Summary

1. The urea clearing power of the kidney in the immediate post-natal period has been investigated in three groups of infants.

2. Group I was a normal group comprising nine male infants. Group II consisted of thirteen male infants, and group III consisted of sixteen female infants. At the commencement of the observation period 3 g. of urea in 30 ml. of water were given by gavage to groups II and III.

3. Urine specimens from groups I and II were obtained by the use of a signalling apparatus. Urine specimens from group III were obtained by catheterization.

4. The urea clearances in group I are considered to be normal clearances, those from groups II and III to be maximum clearances.

5. Comparison of urea clearance between groups I, II, and III suggests that normally at urine minute volumes of 0·05 ml. or less, urea clearance is maximum, but at greater urine minute volumes the urea clearance is normally less than maximum.

6. Comparison of urea clearance between groups I, II, and III and urea clearance in infants over a week old shows that normally less urea is cleared in the immediate post-natal period.

7. Comparison of maximum urea clearance in the immediate post-natal period with the urea clearance of a standard adult having a surface area of 1·73 sq. m. and a weight of 70 kg. shows that on either basis of comparison urea clearance in the immediate post-natal period is less efficient.

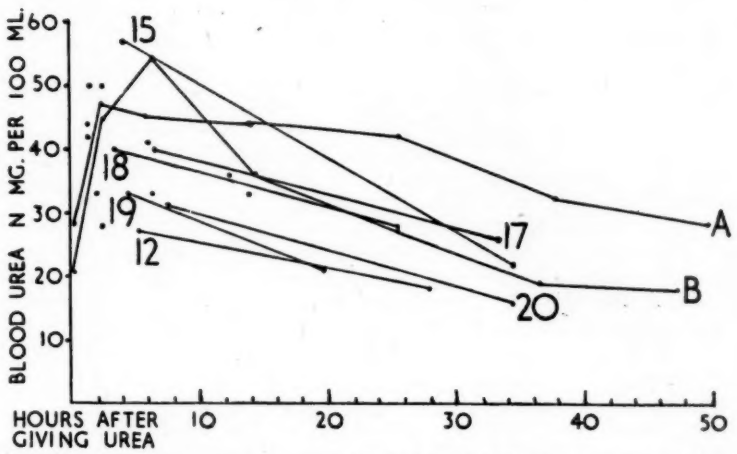

FIG. 6.—Urea nitrogen concentration in blood following administration of urea. Age: A, 44 hours at commencement; B, 54 hours.

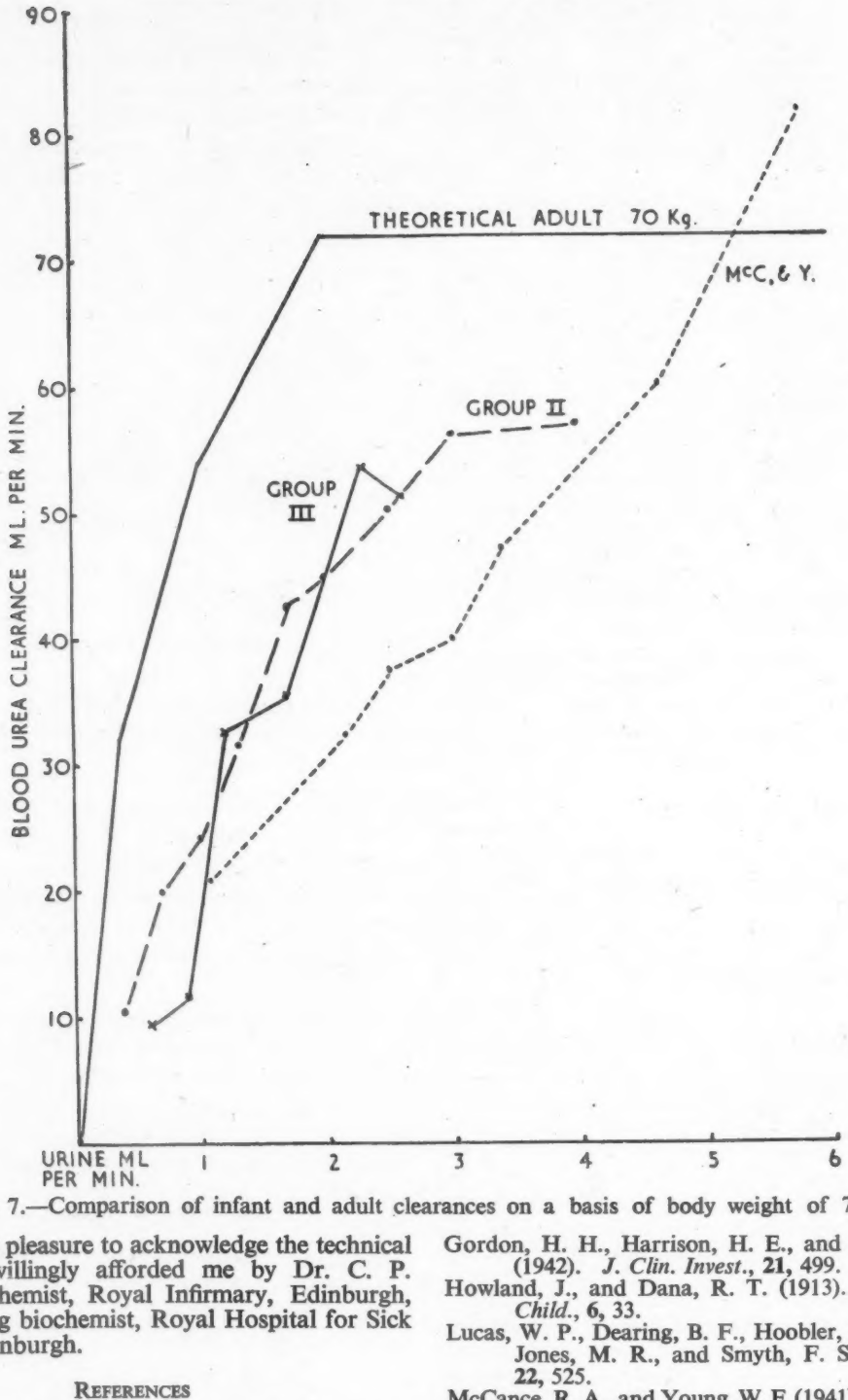

FIG. 7.—Comparison of infant and adult clearances on a basis of body weight of 70 kg.

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THE EARLY DIAGNOSIS OF RICKETS

BY

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With the widespread application of the knowledge of the relationship of vitamin D to rickets, the occurrence of the clinical picture familiar from Glisson's time onwards has nearly disappeared. In its place we are faced with changes brought about by a suboptimal intake of the necessary vitamin. Unfortunately the physical signs on which a diagnosis depends mimic the wide variation of normal to be found in infants. Cecil (1940) thus sums up the position: 'Clinical appraisal of the departure from normal in the rib-cartilage junction is difficult. A common clinical error is to diagnose rickets where no rickets is present.' The reverse is true. The same statement is applicable to the closing of the fontanelle, the eruption of teeth, and the width of the lower end of the radius. 'The clinical diagnosis of rickets based upon enlarged epiphyses and bow-legs is often unreliable.' (Price, 1946).

The radiological appearance of the lower end of the radius and ulna is often accepted as the arbiter. This is open to question, for the British Paediatric Association (1944) in an enquiry into the incidence of rickets in war-time, using a panel of experienced paediatricians and radiologists, found a clinical incidence of 12·5 per cent. to a radiological 0·5 per cent. Rackow (1949) says:

'The wrist joint in the infant is generally accepted by radiologists as being the most satisfactory for x-ray study in the diagnosis of rickets. It offers no technical difficulties in the making of the radiograph and when changes in the bone have occurred they are invariably present at the lower end of the radius and ulna. Being a small joint, all parts remain comparatively close to the film, so that as long as movement is excluded, the definition of bone structure is sharp.

'The florid and active form of rickets is readily diagnosed radiologically, and the diagnostic problem now mainly concerns itself with slighter degrees of rachitic change.

'The early radiological changes in the bone are mainly changes of degree and not of kind. Thus, slight expansion of the diaphyses of the radius and ulna is already present at the lower end of the normal bone. The ulna also normally shows slight cupping; osteoporosis may be simulated by slight over-penetration of the radiograph. For these reasons, and because radiological change of any kind in bone, which is due to systemic disorder, may take several weeks to establish itself, the early radiological diagnosis of rickets may be uncertain and many cases can only be classed as doubtful.'

The plasma-alkaline-phosphatase has been accepted by many observers as a reliable means of detecting active and latent rickets (Cantarow and Trumper, 1945). In this respect, most investigators have used Bodansky's method for determining the phosphatase content of the blood in rickets. It has two disadvantages for routine use in paediatrics in that it requires well over an hour for a determination and it needs 2 ml. of serum. On the other hand, the King-Armstrong method can be completed in twenty-five minutes and requires only 0·4 ml. plasma. An alternative argument in favour of Bodansky's method is that it combines an estimation of the serum inorganic phosphate as well as the phosphatase. However, it has been our experience that the inorganic phosphate in the majority of cases of early rickets is within normal limits although the phosphatase is increased. Barnes et al. (1946) noted that in 40 per cent. of their cases of rickets the calcium and phosphorus levels were normal. Josefsson (1941) has shown that active rickets may be present in spite of normal calcium and phosphorus levels, but in the healing stage the phosphorus level may be low. Thus, there seems to be considerable evidence that the blood calcium phosphorus product is unreliable as a means of detecting early rickets. Because of the arguments presented here, the plasma alkaline phosphatase has been estimated by the King-Armstrong method in all cases of clinically suspected rickets seen at the Belgrave Hospital for Children during the last two and a half years. The normal range is 0-10 units in the adult. Little information was available as to the normal and pathological ranges to be found in young children, for only two references were found which had a bearing on rickets. May and Wygant (1939) considered that rickets could not be diagnosed under 55 King-Armstrong units of phosphatase activity, and on the other hand Corner (1944) put the normal range at 3-10 units with no relation to age, and suggested that readings of 15 units or over were diagnostic of rickets. In our experience, the first was too high and the latter too low. An attempt, therefore, has been made to assess the normal range, to relate the clinical condition to King-Armstrong units of phosphatase activity, and to use the phosphatase content as a guide to treatment.

TABLE 1

ANALYSIS OF CASES OF CLINICAL RICKETS SHOWING PLASMA PHOSPHATASE LEVELS AND RESPONSE TO VITAMIN D

No.	Sex	Vitamin D	Age	Signs	Phosphatase Units		Treatment	Remarks
					Date	No.		
1	F.	Given†	1 yr. 7 months	S+S+**	16 Jan., 1947 19 Feb., 1947 19 Mar., 1947	25 51 14	Calciferol 200,000 units	Radiograph showed epiphyses rachitic
2	F.	?	11 months	B+F1	21 Nov., 1946 28 Feb., 1947	23 18	Radiostoleum 5 ml. daily	
3	M.	None	5 months	B+C+E+	4 Dec., 1946 31 Mar., 1947	24 20	Calciferol 200,000 units	
4	M.	?	1 yr. 3 months	B+S+	4 June, 1947 23 Aug., 1947 5 Jan., 1948 5 April, 1948	30 23 20 17	Adexolin 30 m. daily	
5	M.	?	1 yr. 7 months	B+Bs	7 May, 1947 7 July, 1947	76 17	Calciferol 200,000 by 3	Radiograph showed epiphyses rachitic
6	M.	Given	1 yr. 11 months	B+F+C+	26 July, 1948 1 Sept., 1948	64 29	Calciferol 200,000 units	
7	M.	?	1 yr. 6 months	B+Bs	26 Jan., 1948 1 Mar., 1948	36 21	Calciferol 200,000 units	Radiograph normal
8	M.	?	1 yr. 5 months	B+F+	28 June, 1948 29 July, 1948	38 25	Calciferol 200,000 units	Radiograph normal
9	F.	?	2 yrs. 6 months	B+	16 Jan., 1947 13 Feb., 1947	25 19	Calciferol 200,000 units	
10	M.	?	8 months	B+F+C+	30 Sept., 1946 25 Oct., 1946 24 Nov., 1946	29 42 46	Ostelin 30 m. daily	Radiograph showed recalcifying rickets
11	M.	?	3 yrs. 6 months	Bs	12 July, 1948 4 Oct., 1948	30 20	Calciferol 200,000 units	
12	M.	?	1 yr. 3 months	B+S+F1	29 Apr., 1948 16 June, 1948 13 July, 1948 18 Oct., 1948 20 Dec., 1948	30 42 58 37 18	Calciferol 200,000 by 3	
13	M.	?	1 yr. 11 months	F+Bs	11 Aug., 1948 6 Oct., 1948	44 34	Cod-liver oil dr. 2 daily	
14	M.	Given	1 yr. 8 months	B+B+Bs	6 Aug., 1948 5 Oct., 1948 16 Nov., 1948 28 Dec., 1948	51 30 38 39	Calciferol 200,000 by 3	
15	F.	?	1 yr. 7 months	B+B+BsS+	6 Oct., 1948 15 Nov., 1948 16 Dec., 1948	42 43 22	Calciferol tab. co, t.d.s. (500 units, Vit. D per tablet)	
16	F.	?	1 yr. 1 month	B+E+BsF1	11 Nov., 1948 15 Dec., 1948	38 16	Calciferol 200,000 by 2	
17	M.	?	1 yr. 5 months	B+E+F1	4 Jan., 1948 8 Feb., 1948	46 17	Calciferol 200,000 units	
18	M.	Given	1 yr. 3 months	B+B+	25 Aug., 1948 6 Dec., 1948	58 22	Calciferol 200,000 by 2	
19	M.	Given	1 yr. 9 months	B+E+F+	7 May, 1948 9 June, 1948	32 22	Calciferol 200,000 units	Radiograph showed ? rickets
20	F.	Given	1 yr. 2 months	E+F+	12 Mar., 1947 7 May, 1947 16 June, 1947	36 23 17	Calciferol 200,000 units	Radiograph showed healing rickets
21	F.	Given	1 yr. 4 months	B+Bs		45		Radiograph showed epiphyses rachitic
22	F.	None	1 yr. 4 months	F+F1		33		
23	F.	Given	1 yr.	B+F+F1		49		
24	F.	?	1 yr. 8 months	B+		49		
25	M.	Given	7 months	F+C+F1		36		
26	F.	?	2 yrs. 3 months	B+BsF1		37		

TABLE 1—*cont.*

No.	Sex	Vitamin D	Age	Signs	Phosphatase Units Date	Phosphatase Units No.	Treatment	Remarks
27	F.	None	11 months	B+E+C+		32		
28	M.	None	1 yr. 4 months	B+BsC+		32		
29	F.	None	7 months	B+		30		
30	F.	?	1 yr.	B+F1		27		Radiograph showed epiphyses rachitic
31	M.	None	2 yrs. 3 months	E+F1		30		
32	M.	Given	1 yr. 6 months	B+		26		Radiograph showed epiphyses rachitic
33	M.	Given	4 months	B+C+		26		
34	M.	None	1 yr. 3 months	E+Bs		30		
35	M.	?	2 yrs.	E+BsF1		32		
36	F.	?	2 yrs.	B+E+Bs		26		Radiograph normal
37	M.	None	2 yrs. 1 month	B+F1		32		
38	M.	?	1 yr. 3 months	B+E+		29		
39	M.	Given	1 yr. 3 months	B+F+		29		
40	F.	None	2 yrs. 6 months	B+BsF+		31		
41	M.	?	1 yr. 9 months	B+E+		33		
42	F.	?	1 yr. 6 months	B+Bs		32		
43	M.	?	9 months	B+F+F1		27		
44	M.	None	4 months	F1		37		Radiograph showed epiphyses rachitic
45	M.	Given	1 yr. 8 months	B+F+F1		54		Radiograph showed rachitic changes
46	F.	?	6 months	B+E+F1		30		Radiograph showed epiphyses rachitic

* In the tables:
B+ = beading at the costochondral junction. This was assessed as far as possible on the recommendations of Dalyell and Mackay (1922), and beading has not been indicated unless it could be graded 1½-2 by their standards.
Bs = bossing of the skull.
C+ = craniotabes.
E+ = enlarged epiphyses at the wrists.
S+ = Harrison's sulcus.
F+ = a fontanelle larger than age permits.
F1 = muscle tone poor.

† Where the mother was insistent that cod-liver oil had been given it is stated as 'given'; doubtful evidence has been indicated by a question mark.

Method

The plasma phosphatase was determined in forty-six apparently healthy children from one month to three years old with no clinical signs of rickets. The average obtained for this group was 17 King-Armstrong units with a spread of 11-20. Ten children of three to five years averaged 12 units with a spread of 8-18 units. In thirteen of the controls picked at random, radiographs of radial and ulnar epiphyses appeared normal.

We have not included three cases of florid rickets in which the phosphatase levels fell between 80 and 220 units as diagnostic confirmation was not required.

One of us (F.S.C.) is responsible for the clinical diagnoses in all the cases reported.

Discussion

The contention that rickets cannot be diagnosed under 55 King-Armstrong units of phosphatase activity is not borne out by the findings in the series of cases presented. In most the diagnostic titre lay between 30 and 40 units, and with the institution of specific therapy the response was prompt and marked. On the other hand, it has not been possible to substantiate clearly Corner's claim that rickets could be related to findings in the 15-20 units range. Setting aside the control values given in this paper and considering the problem from different aspects, the following points are put forward to strengthen the view that her figures for normality are too low for the first two years of life. Barnes and Munks (1940) in establishing values for infants

TABLE 2

ANALYSIS OF CASES WITH SYMPTOMS BUT NO SIGNS

No.	Sex	Vitamin D	Age	Signs	Phosphatase Units Date	No.	Treatment	Remarks
1	M.	Given	1 yr. 2 months	Irritable	20 Oct., 1948 19 Nov., 1948	35 27	Tab. Calciferol Co. t.d.s. (5 units, Vit. D. per tab.)	
2	F.	None	1 yr. 9 months	Irritable	14 Oct., 1948 30 Nov., 1948 25 Jan., 1949	29 23 23	Tab. Calciferol Co. t.d.s. (5 units, Vit. D. per tab.)	
3	F.	None	1 yr. 8 months	Irritable Sweats	27 May, 1948 25 June, 1948 28 July, 1948 29 Oct., 1948 27 Jan., 1949	38 24 45 35 17	Calciferol 200,000 by 3	Radiograph normal
4	M.	?	1 yr. 4 months	Head sweats	26 May, 1948 30 June, 1948 26 July, 1948 23 Aug., 1948 20 Sept., 1948 20 Jan., 1949	33 36 35 42 34 26	Calciferol 200,000 by 5	Radiograph showed ? rickets
5	M.	None	9 months	No symptoms	18 Nov., 1946 1 Jan., 1947 23 June, 1947	33 15 17	Radiostoleum 5 ml. daily	Radiograph showed epiphyses rachitic Radiograph showed epiphyses normal
6	F.	None	6 months	Irritable	24 Aug., 1948 23 Sept., 1948	31 16	Calciferol 200,000 units	
7	M.	?	11 months	Irritable	9 July, 1947 7 Apr., 1948	27 20	Adexolin m. 10 daily	
8	F.	None	4 months	Irritable Head sweats	25 Mar., 1948 11 May, 1948	28 20	Adexolin m. 10 daily	
9	M.	None	6 months	Irritable	20 May, 1948 23 June, 1948 13 Oct., 1948	36 58 24	Calciferol 200,000 by 4	Radiograph normal

TABLE 3

ANALYSIS OF CASES WITH SYMPTOMS AND A NORMAL PHOSPHATASE

No.	Sex	Vitamin D	Age	Signs	Phosphatase Units Date	No.	Treatment	Remarks
1	M.	Given	7 months	Irritable Now showed B+F1	10 Aug., 1948 15 Nov., 1948	24 54	No treatment given Calciferol 200,000 by 3	Radiograph normal
2	F.	Given	1 yr. 3 months	Delayed dentition F+ ?	12 Dec., 1947 16 June, 1948 1 Sept., 1948 27 Oct., 1948 24 Nov., 1948	20 32 60 24 22	No treatment given Adexolin ml. 5 daily	Radiograph normal

in Bodansky units have shown that phosphatase activity rises from 7·1 units on the third day to 13·0 units by the fourth or fifth month, and then gradually declines to 11·5 units by the end of the third year, the normal adult range being 1·5-4 units.

Klasmer (1944) in his controls found a variation of 9-15 Bodansky units in children ranging in age from six months to two and a half years. It is not possible to convert Bodansky to King-Armstrong units, but as they both measure phosphatase activity, it is to be expected that the variation in one should be reflected by the other. If Corner's figure of up to 10 ± 5 units normal range for the infant is accepted, then it shows very little difference from the adult normal and does not mirror the rise which other observers have noted for Bodansky's method.

Further, the greatest rate of growth in length in a child, about eighteen inches, occurs during the first three years of life, dropping to less than half that figure for the next three years. It seems reasonable to expect the tremendous epiphyseal activity to be paralleled by a phosphatase activity greater than that found in the static adult. It is thought therefore that the figure of 20 units as the upper limit of normal for the first three years of life given by the control series in this paper is approximately correct.

A phenomenon discussed by Yieh and Wisler (1938) as well as by Josefsson is seen in some of the cases in this series, namely in table 1 nos. 1, 10, 12; in table 2 nos. 3, 4, 9; and in table 3, no. 2. With the institution of vitamin treatment, particularly of the

TABLE 4

ANALYSIS OF CASES CLINICALLY DIAGNOSED AS RICKETS WITH NO BIOCHEMICAL CONFIRMATION

No.	Sex	Vitamin D	Age	Signs	Phosphatase Units Date	Phosphatase Units No.	Treatment	Remarks
1	M.	Given	7 months	B+C+	7 June, 1947	20	Calciferol 50,000 by 3	Radiograph showed epiphyses rachitic
					4 Feb., 1948	16		Radiograph showed improvement
					17 Mar., 1948	31	Calciferol 100,000 by 3	Radiograph showed healing
2	M.	Given	1 yr.	Bs	9 Apr., 1948	20	Calciferol 200,000 units	Radiograph normal
					21 July, 1948	13		
3	M.	Given	8 months	E+S	28 Oct., 1947	18	Calciferol 200,000 by 3	
					31 Dec., 1947	20		
					11 Feb., 1948	20		
4	F.	None	1 yr. 6 months	B+E+	14 Nov., 1947	20		
5	F.	None	2 yrs.	B+BsE+	25 Feb., 1947	21		
6	M.	Given	1 yr. 2 months	B+S	9 May, 1947	22		Radiograph showed ? rickets
7	M.	Given	9 months	B+Bs	25 Mar., 1947	21		
8	F.	Given	1 yr. 5 months	B+BsE+	28 Apr., 1947	22		Radiograph showed slight rachitic change
9	M.	Given	8 months	E+		16		Radiograph showed rachitic changes present
10	M.	None	1 yr. 1 month	B+E+		13		Radiograph showed healing rickets

shock variety, there is first a fall in phosphatase activity, then a secondary rise, finally a slow fall to normal. This is assumed to be associated with the process of healing in more advanced cases. The usual reaction in milder types is a prompt drop to a point either near or within the normal range.

Dikshit and Patwardhan (1946) working on experimental rickets in puppies noted that the phosphatase started to rise slowly from the very beginning of vitamin D deficiency. This is illustrated in table 2 by cases 1-9 when symptoms which might have been due to early rickets were present. None of the usual stigmata were found on physical examination. The phosphatase activity averaged 35 units. It is interesting to note that the phosphatase findings in these very early cases were in the main in keeping with those which had definite signs. It is suggested that although a rise in phosphatase activity is diagnostic of early rickets, it cannot be used in this type of case as an index of the severity of vitamin D deficiency, confirming a similar finding of Morris et al. (1937).

Cases 1 and 2 (table 3) demonstrate the necessity of checking the phosphatase at frequent intervals when the diagnosis is entertained but the biochemical findings are equivocal. Clinical judgment had been swayed by the reported phosphatase level. Consequently no treatment had been given, with the result that three and six months later both biochemical and clinical rickets were present in each case.

Cases 1-10 (table 4) require separate consideration. Case 3 is probably an example of healed rickets in which the physical signs remain but the phosphatase level has returned to normal. In this case, large doses of ' calciferol ' had no effect on the enzymatic activity. This has been suggested as diagnostic of healed rickets by Klasmer (1944). Cases 4-6 are difficult to classify because of a lack of fuller information. They could be cases of active rickets with a borderline phosphatase level, or of healed rickets with persistent physical signs. A dose of 200,000 units of calciferol and a phosphatase estimation three weeks later would probably have settled the point. This reaction is illustrated by cases 1 and 2. Case 8 is probably borderline, and for nos. 9 and 10 no explanation is offered.

No attempt has been made to correlate radiological and biochemical findings, a difficulty experienced by Bodansky and Jaffe (1934) and appearing in this series as well. They found cases with a normal phosphatase content and radiological evidence of rickets, and a review of the cases presented here shows the same inconsistency. Radiological diagnosis of early rickets is renowned for its difficulty, and is one in which error is great even among the most highly skilled observers. The limitations of the radiologist in this respect are noted by Barnes and Carpenter (1937), and it is felt that too much reliance should not be based on x-ray examinations for diagnostic purposes in those cases where, at best, a radiograph can only be expected to show minimal changes.

Summary

An estimation of the plasma-alkaline-phosphatase by the King-Armstrong method in 56 controls gives a range of 11-20 units with an average of 17 for

children between one month and three years of age. Over that age, the average approximates to the figure for adults.

In sixty-four cases of clinical rickets, blood phosphatase levels were evaluated, many of them serially before and after treatment. The most frequent diagnostic titre lay between 25-40 units.

The prompt response to specific therapy is shown. The raised blood phosphatase level due to shock therapy has been noted and discussed. The phosphatase level in very early cases showing symptoms but no signs averages 35 units.

The difficulties of diagnosis in borderline cases are mentioned, and it is suggested that a dose of calciferol, 200,000 units, followed by a further blood phosphatase estimation three weeks later may be of assistance in solving the problem. The difficulties of early radiological diagnoses are stressed, and it is suggested that the discrepancies which occur occasionally in cases of clinical rickets and a normal phosphatase may be due to the persistence of physical signs in healed rickets.

We are indebted to Dr. A. M. Rackow for his assistance in discussing the radiology of rickets.

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A CASE OF CONGENITAL IDIOPATHIC HYPERTROPHY OF THE HEART

BY

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This case is an example of an uncommon malady in which our knowledge of its etiology may be furthered by fully recording each case as it occurs.

The condition is characterized by marked cardiac enlargement and often cardiac failure in an infant or young child, but without evidence of the usual causes of such enlargement.

Case History

A boy, aged fourteen months, was brought to University College Hospital late one night because the parents were alarmed by his rapid breathing, unusual bouts of screaming, and refusal to eat. Two days previously he had returned by car from a seaside holiday, and after the journey appeared unwell and refused to eat. The following day he was still fretful and rather feverish. He had diarrhoea, and vomited on one occasion. On the day of admission he became more miserable, and his breathing was laboured. He was thirsty, but refused food and had bouts of screaming.

His birth had been normal, and the child had been apparently healthy with no previous illnesses until an attack of measles six weeks before admission. He was the first child of a healthy mother who had been well throughout pregnancy, and had not suffered any earlier miscarriages. The father had had ulcerative colitis for many years. There was no consanguinity between the parents, and no history of heart trouble or sudden deaths in childhood on either side of the family.

On admission the child was noticed to be pale and perspiring but without obvious cyanosis or venous engorgement. The temperature was 100° F. and the respiration rate 90 per minute. There was slight injection of the left tympanic membrane but the rest of the upper respiratory tract was normal. In the chest the percussion note was normal, the breath sounds were loud at both lung bases, and no adventitious sounds were heard. The heart sounds were normal and the rate 112 per minute. The heart size was not estimated. In the abdomen the spleen was not palpable and there was no ascites. The liver was palpable three fingers below the right costal margin. Other systems were normal. An x-ray examination of the chest showed well marked cardiac enlargement (fig. 1) and a faint opacity at the left lung base on the lateral view.

His immediate condition was thought to be an early bronchopneumonia, and sulphamezathine was prescribed. The child died six hours after admission.

Pathology. Necropsy was performed seven hours after death by Professor G. R. Cameron.

The body was that of a fairly well nourished male child looking his age of fourteen months. There was slight oedema of the ankles and legs. The pupils were equal and average in size, and the conjunctivae clear. There were no icterus, palpable glands, skin rashes, or herniae. The lips were not cyanosed. There was little post-mortem staining.

HEART. Its weight was 135 g. (normal 41 g.), and 60 ml. of clear, straw-coloured pericardial fluid was found. There was no pericarditis, and little

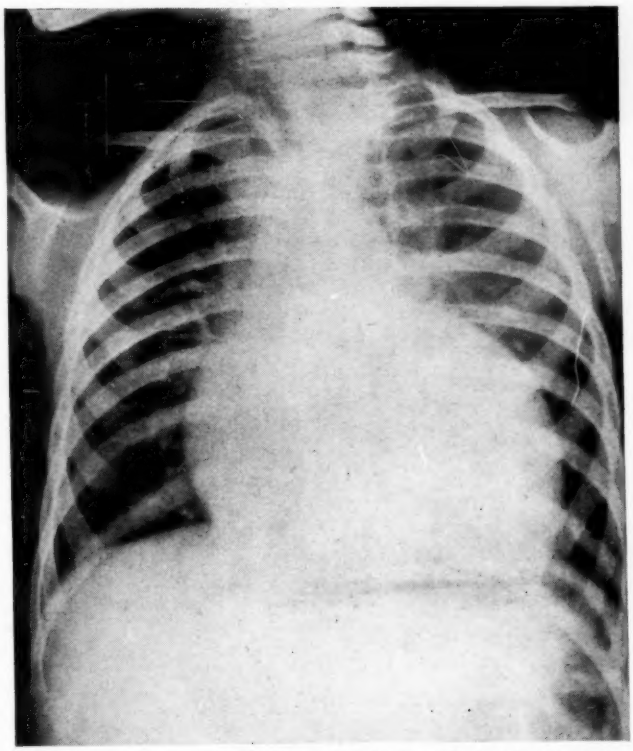

FIG. 1.—Radiograph of chest showing cardiac enlargement.

epicardial fat. There were numerous small and medium-sized fresh subepicardial haemorrhages at the base posteriorly along the course of the main coronary vessels, and crops of petechiae at the apex posteriorly, also some ecchymoses on the ascending aorta. Hypertrophy and dilatation of the ventricles was very marked, particularly of the left ventricle wall, which was 14 mm. thick, and the right 3·5 mm. (fig. 2). The heart muscle was firm and free from obvious fibrosis. The iodine test for glycogen was negative. The aortic valves were normal. The mitral valves were competent, showing some tiny pin-point firm areas at the margin of the valve flaps. There were similar reddish areas at the edges of the tricuspid valve. The foramen ovale was closed. There was only post-mortem clot in the ventricles. The aorta was free from atheroma throughout. The ductus arteriosus was closed. There was no coarctation. The large veins near the heart contained post-mortem blood clot.

LUNGS. Between 60 and 90 ml. of clear fluid were found in both pleural cavities with partial collapse of the right lung. The lungs were greyish in colour, air-containing, congested, and free from consolidation, with signs of acute bronchitis. The hilar and tracheo-bronchial glands were prominent and fleshy but not grossly enlarged. The trachea contained a little mucopus. The larynx was normal.

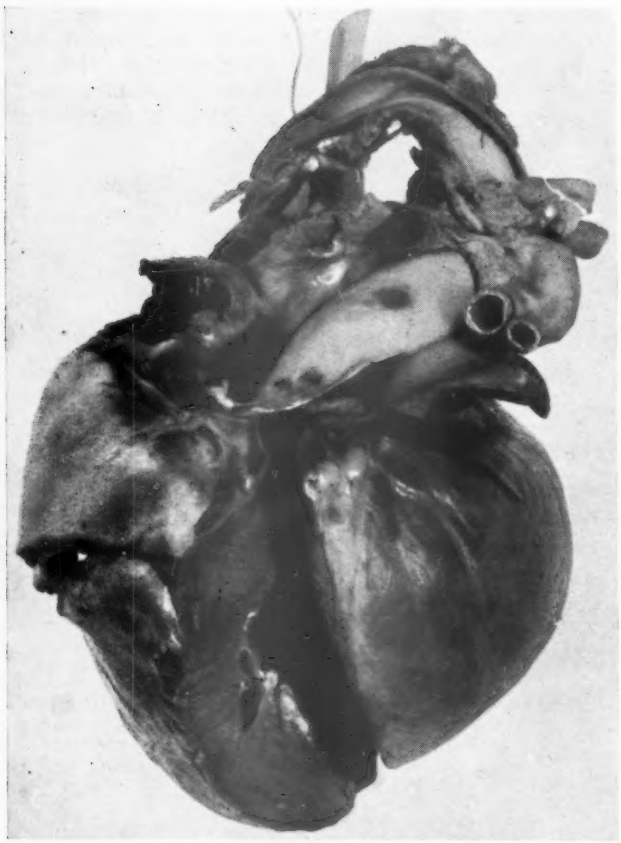

FIG. 2.—Photograph showing extraordinary thickness of the wall of the left ventricle (14 mm.) compared with that of the right ventricle (3·5 mm.), and the presence of subepicardial and adventitial haemorrhages.

LIVER. Weight was 285 g., and the organ was of average size, fatty but firm with no perihepatitis. The hepatic veins and portal vein were normal. The gall bladder was distended containing thick, greenish bile, and the wall was normal. The bile ducts were patent. The pancreas was normal.

SPLEEN. The weight was 25 g. and it was of average size, firm and dark red, with no perisplenitis. The artery and vein were normal.

KIDNEYS. Their weight was 50 g. and they were of average size with a capsule which stripped easily and cleanly, disclosing a dark red, firm, smooth surface, and no cysts. The cortex was broad and the medulla showed a streaky congestion, but the pattern was clear. Small arteries were not thickened. There was little pelvic fat. The tips of the papillae were very red. Both pelves showed congested vessels and a few petechiae. The ureters, bladder, prostate, and genital organs were all normal. There was a little urine in the bladder which contained albumen but no sugar or blood.

DUCTLESS GLANDS. The pituitary, thymus, thyroid, and adrenals were all normal.

ALIMENTARY CANAL. The tongue was normal. The nasopharynx was congested with very large soft tonsils. The oesophagus was empty. The stomach contained a moulded milk clot, and the wall was uniformly reddened and smooth. Only a little mucus was present, but no free blood. The first part of the duodenum showed a congested wall. The small and large intestines showed patches of congestion which were not very severe and free from ulceration. The mucous coat of the large intestine seemed swollen. The mesenteric glands were prominent, fleshy and mildly congested, but not very large. There was a moderate amount of fat in the mesentery and omentum. Clear, straw-coloured ascitic fluid (60 ml.) was present.

BRAIN. There was slight congestion of the membranes and brain substance with a few petechiae scattered throughout the white matter of the cerebrum and around the dentate nucleus of the cerebellum. No areas of softening were found, and no oedema. The choroid plexus was normal, and the ventricles clear and not dilated. No haemorrhage had occurred in the brain stem and there was no pressure cone. The middle ears were almost dry with no pus. The venous sinuses contained post-mortem clot and fluid blood.

BONES. The red bone marrow in the femurs, ribs, and sternum was ample and no obvious abnormalities were apparent. The cranial bones showed a congenital deficiency in the region of the left occipital bone about 1 cm. above the foramen magnum. The gap in the bone was bridged by a thickened periosteum and dura, so that any herniation of the cerebellar lobe on that side was prevented.

There was no apparent leakage of cerebrospinal fluid here.

We concluded that this was a case of congenital idiopathic hypertrophy of the heart, associated with bronchitis and bronchiolitis, the latter probably the result of the attack of measles.

Laboratory investigations. The brain, lungs, kidneys, spleen, lymph glands, adrenals, prostate, and several sections from various parts of the intestinal tract were all normal on microscopy.

The liver was of normal architecture without any increase of fibrous tissue in the portal tract or cellular infiltration, and there was no venous congestion. The peripheral liver cells in the lobule were normal but most of the central ones contained some vacuoles. Cloudy swelling was absent. After some two months' fixation in formalin solution a Best's carmine stain showed a very small amount of glycogen in tiny granules in the normal liver cells but not in any of the vacuoles. Though a fat stain was not made, the gross appearance of the liver and the type of vacuoles suggested that there was fatty infiltration.

All the muscle fibres of the heart were much larger than one would expect in a child of this age. In places, giant fibres, twice the thickness of the rest, could be seen. The fibres appeared longer than normal, but these were not measured because of the difficulty in gauging the exact length of the fibres in a section.

In order to show the hypertrophy of the muscle fibres, microphotographs (fig. 3) were taken of the section of this heart and that of another boy of the same age in good general condition, who died after a few days' illness from pneumococcal meningitis. Both sections were taken from the same area of the left ventricle on the anterior surface midway between the apex and the aortic valve.

TABLE

Hypertrophied Heart	Control
Weight, 135 g. Diameter of most muscle fibres, 30μ. Diameter of giant fibres, 50-65μ.	Weight, 47 g. Diameter of muscle fibre, 5-8μ.

Karsner, Saphir, and Todd (1925) in a study of hypertrophy and atrophy in adult heart muscle give the average diameter of an adult muscle fibre as 31·5μ. They found that in hypertrophy the size of individual fibres increased but not their number, and that therefore there was no true hyperplasia of muscle fibres. I was not able to estimate in this case whether there was any hyperplasia with increase in the number of muscle fibres.

The nuclei were of a normal vesicular type, but most were more rounded than the usual elongated, oval shape. The nuclei in the giant muscle fibres were round and irregular with an easily visible nucleolus, and cytoplasm was abundant and clear in some but dark in others.

The muscle fibres did not show hyaline change, cloudy swelling or fragmentation, nor were they of irregular shape. Heidenhain's iron haematoxylin stain showed normal muscle striation. In places many fibres showed small vacuoles, usually near the nucleus. A Best's carmine stain two months after fixation in formalin solution revealed a small amount of glycogen in the form of small red granules in the fibres, but not in any of the vacuoles. A Sharlach red fat stain demonstrated a normal amount of intracellular fat in fine droplets.

The myocardium was free from interstitial fibrosis and cellular infiltration. The endocardium of the ventricles and auricles was normal, and there was no pathological change in the coronary arteries or their finer branches.

Discussion

It is well to bear in mind that a frequent cause of apparent cardiac enlargement in childhood is the normal broadening of the heart shadow in expiration. Kypho-scoliosis of the spine and depression of the sternum may flatten or displace the heart making it appear big. Acute and chronic pulmonary disease, may result in a large heart and in cardiac failure. Pulmonary collapse, asthma, or emphysema may lead to this enlargement. A severe illness, such as septicaemia, or the extra load and anoxia of severe anaemia, will also cause an increase in the size of the heart. A very large heart in early childhood is usually due to congenital morbus cordis. In the absence of cyanosis, however, many types can be excluded, and an interatrial septal defect, a large ventricular septal defect, or aneurysm of the pulmonary artery, are unlikely without a cardiac murmur. Palpable femoral pulses would exclude coarctation of the aorta. The anomalous origin of one of the coronary arteries from the pulmonary artery will result in a very large heart, without a heart murmur.

Rheumatic pancarditis is rare under two years of age, but diphtheritic myocarditis is a potent cause of heart enlargement and failure. At necropsy little may be seen beyond dilatation and a flabby appearance, and there is no hypertrophy. Microscopically the pathology is seldom very marked. Diffuse hyaline change with occasional fragmentation in the muscle fibres and fatty degeneration can be found.

There was nothing to suggest that this patient had diphtheria. But heart enlargement and myocarditis have been known to follow a number of other common specific fevers, and this child had had measles, from which he recovered well, six weeks previously. The pathological changes in myocarditis which occur during specific fevers and after poliomyelitis do not show the hypertrophy found in the present case. In these types of myocarditis

dilatation with hyaline change and some lymphatic infiltration is found in the myocardium. Myocarditis due to the sulphonamides has been described in which the infiltrating cells are eosinophils and large mononuclear cells. The absence of interstitial cellular infiltrations also excludes trichiniasis.

In Fiedler's isolated myocarditis a diffuse inflammatory change occurs in the myocardium, but as a rule the endocardium and pericardium are normal. The inflammatory cells may be lymphocytes or eosinophils. Some perivascular fibrosis, and occasionally granulomatous necrosis with giant cells, occurs. This condition has been described in children as well as in adults by Everley Jones and Marshal (1948), and Saphir, Wile, and Reingold (1944).

Kugel and Stoloff (1933) reviewed the literature of idiopathic cardiomegaly. One group of these cases showed an interstitial myocarditis characterized by hypertrophy of the ventricular walls, particularly on the left side, thickening of the endocardium of the left ventricle and auricle, and, on cutting the muscle, greyish streaks of atrophied and degenerate muscle could be seen. Microscopically these areas showed replacement by fibrous tissue and round cell infiltration. The majority of these children were under two years old at death, but myocarditis could reasonably be excluded in the present case.

Pallor, or greyish cyanosis, limpness and dyspnoea, venous engorgement and enlargement of the liver, a slight fever and leucocytosis together with enlargement of the heart are the clinical features of paroxysmal tachycardia, but the pulse in the present case was 120 per minute instead of 240 to 300. The enormous cardiac hypertrophy also excluded paroxysmal tachycardia.

Von Gierke's disease and rhabdomyomatosis of the heart can produce cardiomegaly in young children. The former is characterized by enlargement of the liver, ketonuria, a low blood sugar, infantilism, and manifestations of hypoglycaemia. Also heavy glycogen storage occurs in the liver as a rule, probably due to a disturbance in the enzyme system responsible for the reversible conversion of glucose through glucose-phosphate to glycogen. Only in a few cases is cardiomegaly seen with marked glycogen deposition, and it is suggested that in this variety of von Gierke's disease another part of the enzyme system is at fault, for muscle glycogen is broken down to lactic acid or carbon dioxide and water. The present case did not show an excess of glycogen in the tissues when tested with iodine at necropsy, and very little was seen in the histological sections. Van Creveld (1934) has drawn attention to the observation that glycogen in von Gierke's disease is extraordinarily stable even after a long period in watery fixatives.

In rhabdomyomatosis of the heart, single or multiple yellowish-white, discrete tumours are found in the heart muscle, and in them the muscle fibres are grossly distended and distorted with glycogen. The interstitial tissue is not increased and there is no inflammatory reaction. It is of interest to note that Batchelor and Maun (1945) found tuberose sclerosis of the brain in 50 per cent. of reported cases in their review of rhabdomyomatosis of the heart.

Beri-beri is known to cause a very large heart, oedema, and cardiac failure. The heart wall is usually thin and the myocardium degenerate in places, many muscle fibres being fragmented, spiral-shaped or just an amorphous eosinophil mass. Allibone and Baar (1946) described a case occurring in England in a child. There was no history of malnutrition in my case nor is the histology similar.

Kugel and Stoloff (1933) collected seventeen cases from the literature of hypertrophy of the heart without other pathological changes. In eight of these there was enlargement of the individual muscle fibres. Howland (1919) reported five cases with the same condition but in only one were the heart fibres increased in size. Four of their cases showed left ventricular hypertrophy and in the fifth it was bilateral, the right side being more hypertrophied than the left. He referred to two cases reported by Simmonds (1896) and Odendorfer (1906) in which gross hypertrophy of the heart was present in still-births. In the present case the diagnosis would appear to be that of idiopathic hypertrophy of the heart.

Summary

After a short illness with screaming, dyspnoea and anorexia, a child died suddenly from cardiac failure.

Post-mortem examination showed gross enlargement and hypertrophy of the heart, particularly of the left ventricle. Other systems were normal, except for some bronchitis.

Microscopy showed that there was gross hypertrophy of individual muscle fibres without any other pathological change in the heart.

I wish to thank Dr. R. Hardy and Professor G. R. Cameron, F.R.S., for their help, and Dr. B. E. Schlesinger, O.B.E., for allowing me to publish this case.

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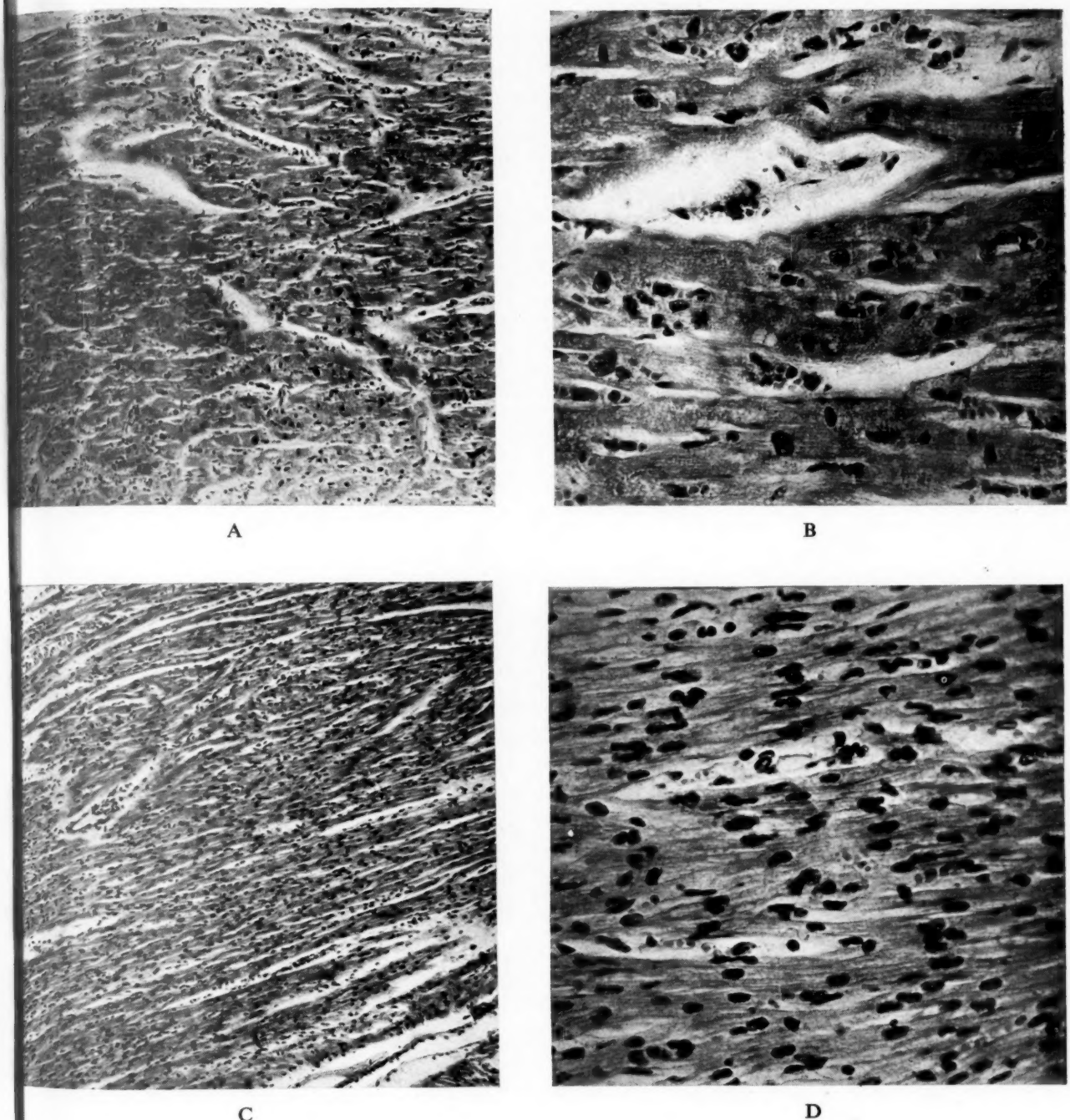

Fig. 3.—A(x65) and B(x310) show sections of left ventricle in the case described of congenital idiopathic hypertrophy of the heart. C(x65) and D(x310) show comparable areas of left ventricle in the control. Comparison of the low power sections shows that the muscle fibres are thicker in the case of idiopathic hypertrophy of the heart. The nuclei are sparser, and many dark staining large ones can be seen. The high power sections demonstrate better the difference in thickness of the muscle fibre and the variable size of the nuclei between the hypertrophied heart and the control.

THRUSH IN INFANCY

BY

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Thrush is a disease which has been known since earliest times but its fungoid nature was not recognized until one hundred years ago when Robin (1853) included the micro-organism in the group of oidium albicans.

Thrush is usually regarded as a relatively mild parasitic infection of the mouth, especially liable to occur in debilitated children. Trousseau (1869) described it as 'the local expression of a very bad state of the whole system.' Thrush may, however, become a more serious condition by extension to the pharynx, bronchi, oesophagus, or even through the blood stream to such organs as the kidney.

Thrush lesions in infants involving the oesophagus and responsible for severe clinical manifestations have been described by Ebbs (1938) who observed twenty-eight cases of oesophagitis in three years, twenty-two of which were caused by monilia albicans. Monilia oesophagitis was also described by Reye (1941) who stressed the diagnostic difficulties of this lesion in necropsy material and the relative frequency of this condition in infancy.

Ludlam and Henderson (1942) drew attention to the high incidence of thrush infection in the neonatal period. In a series of eighteen necropsies they found that thrush lesions had spread to the pharynx in eight cases and that the oesophagus was involved in seven cases. Anderson et al. (1944), investigating the incidence and source of thrush infections, confirmed its high incidence in the newborn.

The present observations were carried out during a period of twelve months in which routine necropsies were performed on twenty-eight infants under four weeks of age and on 176 infants between the ages of one and twelve months. In seven of the twenty-eight neonates and in nineteen of the older infants, pharyngeal or oesophageal thrush lesions were found. The high incidence of these lesions has prompted us to record our findings.

History and Clinical Features

An analysis of the previous history of our cases confirmed the observation of other clinicians that bottle-fed babies and babies of low vitality are especially prone to develop thrush. Only three cases were wholly breast-fed, seven were bottle-fed from birth, and fifteen were bottle-fed by the age of six weeks. Twenty-two babies were born at full-term, but the birthweights of five of these were below 7 lb.; two babies were born prematurely, their birthweights being 5 lb. 4 oz., and 4 lb. 3 oz.

On admission to hospital thrush lesions were visible on the buccal mucous membrane in nine cases, dehydration was noted in fourteen cases, and diarrhoea and vomiting or vomiting alone occurred in eighteen cases. The vomiting associated with thrush lesions may be projectile and simulate congenital pyloric stenosis, as in two of our cases, but more commonly regurgitation or dribbling from the mouth occurs shortly after feeds. Refusal of feeds was present in four cases.

The commonest findings in the seven newly born infants were visible mouth lesions (six cases), vomiting (four cases), dehydration (four cases), and refusal of feeds (three cases).

While in hospital dehydration was encountered as a serious and recurrent complication in twenty-two of these twenty-six cases, and necessitated intravenous fluids on one occasion in fifteen cases, and more than once in seven cases. The sudden onset of toxaemia was another striking feature and it developed within three days of admission in eleven cases. The development of purulent otitis media was also noted in ten cases. In three cases (Nos. 155, 169, 226) there was vomiting of dark brown material which contained blood. A rise in temperature was not recorded except as a terminal event. Sudden collapse, dyspnoea, and cyanosis shortly after a feed occurred in six cases and is related to the finding of food material in the bronchial tree at necropsy.

The early diagnosis of thrush in infants and the newly born may be difficult clinically, especially when visible oral lesions are absent. Routine mouth swabs from all babies admitted to hospital may be of value in early diagnosis, for it is known that in many cases culture is positive for monilia albicans in the absence of visible lesions.

Pathology of pharyngo-oesophageal thrush. Oral thrush is easily recognized at necropsy, unless the patient has been treated with gentian violet or the oral cavity has been plugged with cotton wool after death. As post-mortem oral plugging was carried out as a ward routine, the absence of visible oral lesions in this series was not considered significant. In five cases, however, in which neither gentian violet treatment nor post-mortem plugging

had been carried out, no oral lesions were found, although severe oesophageal changes were present. Pharyngo-oesophageal thrush occurs in milder cases as whitish spots, distributed mainly in the pyriform recesses and the narrow parts of the oesophagus. In the more advanced cases the lesions form large confluent patches which, like the small spots, can be wiped off. In the severe cases, thick pseudomembranes are formed and, if removed, an ulcerated, often bleeding, base is exposed. These lesions present no diagnostic difficulties. In a large number of cases, however, haemorrhages cause the lesion to assume a dirty, greyish-brown colour and sloughing of the pseudomembrane occurs. The presence of gastric contents in the oesophagus and post-mortem digestion of the superficial layers, particularly in cases where the thrush lesion is confined to the distal third of the oesophagus, may make the naked eye diagnosis difficult, if not impossible, as in case 169. In such cases bacteriological and histological examination are necessary to reveal the nature of the lesion.

The histological picture varies according to the severity of the lesion. In the early lesion (fig. 1) there is oedema of the stratified epithelium; mycelia and spores can be seen extending between the epithelial cells and often reaching and perforating the basal membrane. A felt of mycelial threads and spores is superimposed on the epithelium and may contain epithelial debris, red blood cells, and later, masses of Gram-positive and Gram-negative cocci and bacilli. There is generally, even in mild lesions, congestion and dilatation of the submucous capillaries. In more severe lesions (fig. 2), the mucosa is ulcerated and mycelial strands extend to and beyond the muscularis mucosae, and the submucosa shows infiltration with inflammatory cells, which are mainly mononuclear cells, lymphocytes, and less frequently, polymorphs. Capillary haemorrhages are often present. The inflammatory reaction usually extends far beyond the ulcerated area. In severe lesions a thick pseudomembrane is formed consisting of the sloughed-off mucosa, masses of mycelia and spores, and large numbers of organisms. The mycelium may extend beyond the muscularis mucosae and involve the muscular coat. We have found mycelia outside the muscular coat in sections in which the lesion involved the epithelium only. When post-mortem digestion has occurred the diagnosis of thrush lesions may be difficult. Infiltration with inflammatory cells and congestion of the submucosa will draw attention to the possibility of an underlying thrush infection and serial sections may reveal spores or mycelial threads. Gram-stained sections are of help as spores and hyphae generally give a Gram-positive reaction, but at times the organisms do not take the stain uniformly. Spores may be mistaken for lymphocytes in sections stained with haematoxylin and eosin. Fuentes' method (1946) for differentiating monilia albicans in tissues has not given satisfactory results in our hands.

Continued growth of the fungus and infiltration of the underlying tissue after the death of the patient has been observed in a number of cases, and the absence of any tissue reaction has been taken as evidence of post-mortem spread.

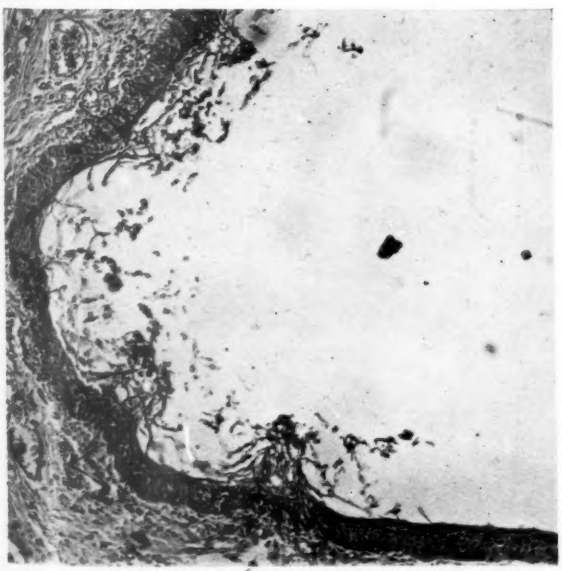

FIG. 1.—Early lesion of pharynx (case 146). × 95.

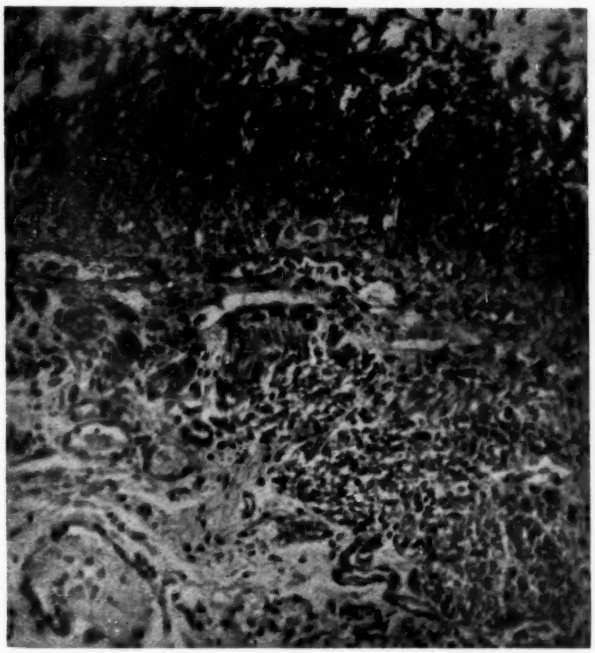

FIG. 2.—Inflammatory reaction of oesophagus involving submucosa (case 169). × 120.

The diagnosis of oesophageal or pharyngeal thrush was made on naked eye evidence alone in six cases of the series; in a further six cases by bacteriological examination; in three cases by histological examination without bacteriological examination; and in the remaining cases by bacteriological and histological examination.

The bacteriological diagnosis was made by examination of smears from the lesions and culture on Sabouraud's medium and blood agar plates both directly and after ether treatment of a serum broth culture to eliminate Gram-negative organisms (Pearce, 1946).

Complications of Pharyngo-oesophageal Thrush

Involvement of the respiratory system. Regurgitation of feeds into the air passages occurs frequently in patients with pharyngo-oesophageal thrush and the incidence of this complication in our series was high. Eleven cases showed microscopical evidence of aspiration pneumonia and in a further six cases the aspirated material blocked the air passages, thus causing sudden death (see table). During the same period of observation fifty-nine children in the same age group died from gastro-enteritis or marasmus, and in twenty-one of these aspiration had occurred. In seventy-two infants who died from various other conditions evidence of aspiration was found in eight cases only. The histological examination of the lungs may reveal aspirated material containing monilia albicans and other organisms covering the bronchial mucosa or present in the alveolar lumen. Occasionally, there is invasion of the bronchial wall by the mycelium, with inflammation and necrosis of the wall (fig. 3) and peribronchial pneumonia.

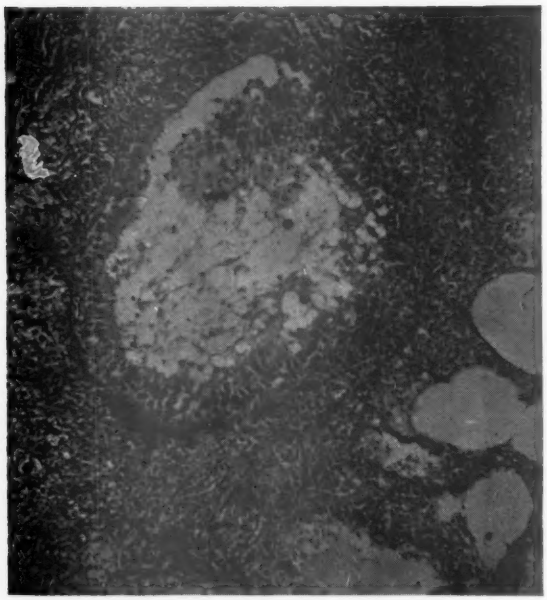

FIG. 3.—Thrush lesion of bronchus with monilial hyphae penetrating bronchial wall (case 169). × 120.

Most frequently the typical picture of aspiration pneumonia is found, and monilia may or may not be present in the alveolar exudate.

The following cases show the typical features of these respiratory complications.

CASES 121 AND 122. These infants were three weeks old and dehydrated. The pyriform recesses were coated with a thick layer of thrush, and in case 121 there was patchy involvement of the oesophagus. In both cases the trachea and main bronchi were blocked with gastric contents. The liver was fatty in case 122, and showed slight fatty changes and small foci of erythropoiesis in case 121.

CASE 174. This infant was three weeks old, wasted, and deeply jaundiced. A confluent brown stained membrane covered the distal oesophagus, and there was a little altered blood in the stomach. Small areas of atelectasis and haemorrhagic consolidation were scattered throughout the lungs. The liver was of normal size and yellowish brown in colour.

Histological examination showed that in the oesophagus large sloughing areas of mucosa were replaced by masses of necrotic cells, monilia, and red blood cells. Hyphae extended into the submucosa, which showed oedema and cellular infiltration. There was oedema and cellular infiltration of the adventitia, extending into the substance of the diaphragm. No organisms were visible in the adventitia.

Involvement of pleura. Extension of the inflammation through and beyond the muscular coat of the oesophagus may, in some cases, lead to direct spread of infection into the pleural sac. In the following two cases (Nos. 123 and 215) empyemata were found at necropsy and we consider that direct spread from the oesophagus was the probable cause. It is also possible that the empyemata were secondary to lung infection.

CASE 123. The child, a girl aged four months, was dehydrated and jaundiced. There was an empyema of the right pleural sac causing compression of the lower lobe and fibrinous pericarditis was also present. The thrush lesion involved the upper third of the oesophagus and there was post-mortem digestion of the distal third. Pus was present in the tympanic cavities and mastoid air cells.

Histological examination showed extensive sloughing of the mucosa of the upper third of the oesophagus. A dense felt of mycelia, spores, and a large variety of organisms and necrotic debris covered the exposed muscularis mucosae which was penetrated by hyphae. Inflammatory infiltration of the submucosa was present. In the distal third the mucosa and submucosa were largely missing owing to post-mortem digestion, but where present the submucosa showed oedema and infiltration with mononuclears, but mycelia or spores could not be demonstrated. The outer coat of the oesophagus showed identical inflammatory changes. Bacteriological examination revealed the presence of

TABLE

ANALYSIS OF NECROPSIES ON 26 INFANTS WITH THRUSH LESIONS

Necropsy number	Age on admission	Sex	Birth-weight	Type of feeding	Site of thrush lesions (post-mortem)	Evidence of inhalation of gastric contents
63	Four months	M.	7 lb. 11 oz.	Breast-fed 1 month, then 'Ostermilk,' then National Dried Milk.	Pharynx: mouth	Vomit in bronchial tree (massive)
72	Eight weeks	F.	7 lb. 2 oz.	Breast-fed	Mouth: oesophagus kidney	Aspiration pneumonia
82	Three weeks	M.	7 lb. 13 oz.	Breast fed 2 weeks, then 'Ostermilk.'	Mouth: oesophagus	Haemorrhagic pneumonia
84	Four weeks	F.	6 lb. 5 oz.	Breast-fed 1 month, then 'Cow and Gate'	Mouth: oesophagus	Haemorrhagic pneumonia
89	Eight weeks	F.	6 lb. 6 oz.	Breast-fed 5 weeks, then 'Ostermilk'	Mouth: pharynx: oesophagus	Vomit in bronchial tree
121	Three weeks	F.	4 lb. 3 oz.	Breast-fed 2 weeks, then 'Cow and Gate'	Mouth: pharynx: oesophagus	Vomit in bronchial tree (massive)
122	Two weeks	M.	6 lb.	'Cow and Gate'	Mouth: pharynx	Vomit in bronchial tree (massive)
123	Ten months	M.	—	Breast-fed 1 month; then National Dried Milk	Oesophagus: left mastoid	—
141	Nine weeks	F.	5 lb. 4 oz.	National Dried Milk	Oesophagus	Vomit in bronchial tree
142	Three months	M.	6 lb. 8 oz.	Breast-fed 6 weeks, then National Dried Milk	Mouth: pharynx	—
146	Three weeks	F.	5 lb. 10 oz.	Breast-fed 4 days, then National Dried Milk	Mouth: pharynx	—
147	Four weeks	F.	7 lb.	Breast-fed with supplements of National Dried Milk	Mouth and pharynx Tonsils	Vomit in bronchial tree
155	Five weeks	F.	7 lb.	Breast-fed	Mouth: oesophagus	—
156	Eight months	M.	—	National Dried Milk	Pharynx: oesophagus	Vomit in bronchial tree
169	Twelve months	M.	7 lb. 12 oz.	Breast-fed	Oesophagus: kidney: ileum	Aspiration pneumonia
174	Three weeks	M.	6 lb. 7 oz.	Breast-fed 4 days, then National Dried Milk	Oesophagus	Haemorrhagic pneumonia
181	Ten weeks	F.	6 lb. 13 oz.	Breast-fed, 6 weeks, then National Dried Milk	Oesophagus	Vomit in bronchial tree (massive)
184	Ten months	M.	—	—	Oesophagus	Vomit in bronchial tree (massive)

TABLE (*continued*)

Necropsy number	Age on admission	Sex	Birth-weight	Type of feeding	Site of thrush lesions (post-mortem)	Evidence of inhalation of gastric contents
190	Twelve months	M.	—	National Dried Milk	Pharynx: oesophagus left mastoid	—
192	Seven months	M.	6 lb. 9 oz.	Breast-fed 1 month, then National Dried Milk	Oesophagus	—
206	Seven weeks	M.	8 lb. 8 oz.	Breast-fed 3 weeks, then National Dried Milk	Oesophagus: right mastoid	Haemorrhagic pneumonia
212	Nine months	M.	—	National Dried Milk	Mouth: oesophagus: right mastoid	Vomit in bronchial tree (massive)
215	Five months	F.	7 lb. 12 oz.	'Cow and Gate'	Oesophagus	—
226	Four months	F.	7 lb. 7 oz.	Breast-fed 5 weeks, then National Dried Milk	Oesophagus	Aspiration pneumonia
235	Three months	F.	7 lb. 10 oz.	Breast-fed 1 month, then 'Cow and Gate'	Mouth: oesophagus	—
254	Ten weeks	F.	7 lb. 12 oz.	Breast-fed 1 month, then National Dried Milk	Oesophagus: lungs	—

B. Friedländer and Ps. pyocyanea in the mastoid pus, empyema fluid, and the oesophagus. Monilia albicans was found in mastoid pus and the oesophagus only.

CASE 215. The child was a girl, aged six months with generalized oedema. There was an extensive ulcerative thrush lesion of the oesophagus and a large amount of greenish, gelatinous pus in the right pleural sac with compression of the lower and parts of the upper lobe. The left lung and pleura showed no abnormality.

Histological examination of the distal third of the oesophagus revealed thrush ulceration involving the mucosa in its entire circumference and it extended in places into the muscularis mucosae. The submucosa showed no inflammatory reaction, but outside the muscular layer there was dense infiltration with mononuclears, polymorphs, and lymphocytes. The infiltration extended into the adherent pericardial sac. Histological examination of the right lower lobe of the lung showed atelectasis and congestion. The pleural exudate consisted mainly of mononuclear cells and scanty polymorphs and a few Gram-positive cocci but no monilia. Culture of the oesophageal lesion yielded monilia albicans, staphylococcus aureus (coagulase-positive), non-haemolytic streptococci, and B. proteus. Monilia albicans, staphylococcus aureus, and non-haemolytic streptococci were grown from the pleural pus.

Septicaemia. Monilia albicans is a parasite thriving on the exposed surface of the alimentary tract and producing superficial ulceration. Extension of the lesion in width and depth may expose a large area to the action of staphylococci and other organisms normally present in the upper alimentary tract, with subsequent septicaemia or pyaemia. In five of our cases pyaemic abscesses were found in various organs. Staphylococci were isolated in two cases and in three cases there was a mixed bacterial flora, including staphylococci, enterococci, coliform bacilli, and Ps. pyocyanea.

CASE 254. The child, a girl, was aged four months and had generalized oedema. The distal two-thirds of the oesophagus was covered by an adherent, dirty, brownish-red membrane. Mucopus was present in both tympanic cavities and mastoid air cells. The lungs contained numerous small atelectatic areas.

Histological examination revealed that the mucosa of the oesophagus was completely and uniformly necrotic and replaced by a mass of cellular debris, hyphae, and spores. The muscularis mucosae was invaded by hyphae and the submucosa was congested. There was scanty cellular infiltration of the outer coat of the oesophagus which also contained a few spores and hyphae. The kidneys contained small pyaemic staphylococcal abscesses. In the lungs, a film of aspirated material covered the bronchial epithelium and spores and bacteria were

present in the alveoli. There was no inflammatory reaction.

Monilia albicans, staphylococcus aureus (coagulase-positive), coliform bacilli, and enterococci were isolated from swabs of the oesophagus, mastoid air cells, and bronchi.

Monilaemia. We have found evidence of metastatic lesions in the kidneys in two of our cases.

CASE 72. This was a girl of nine weeks who was emaciated and dehydrated. Petechiae were present on the abdominal skin and the buttocks were excoriated. There was thick pus in the tympanic cavities and mastoid air cells. Thrush of the tongue and buccal mucosa and patchy thrush lesions in the distal third of oesophagus were present. Numerous foci of aspiration bronchopneumonia were scattered throughout the lungs. The cortex of the kidney was yellowish brown and small miliary granules were prominent on the cut surface.

On histological examination the kidney (fig. 4) showed numerous miliary granulomata consisting of a centre formed by masses of spores in small arteries or tubules, surrounded by collections of mononuclear cells.

CASE 169. This child was a boy of twelve months who had pyaemia with multiple embolic abscesses in the lungs and kidney, and purulent fluid in the posterior horn of the lateral ventricles. In addition to the pyaemic (staphylococcal) abscesses, granuloma-like lesions containing hyphae and spores were found in the kidneys (fig. 5).

The dissemination of thrush lesions to various organs by the blood stream has been mentioned by several authors. The total number of cases reported

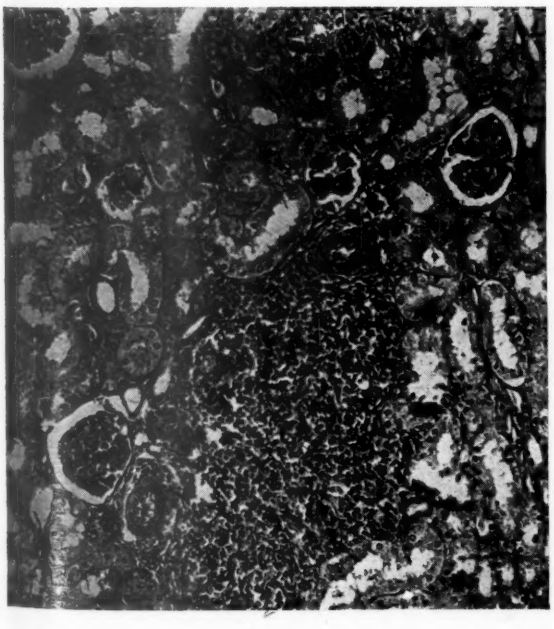

FIG. 4.—Thrush lesion of kidney (case 72). × 85.

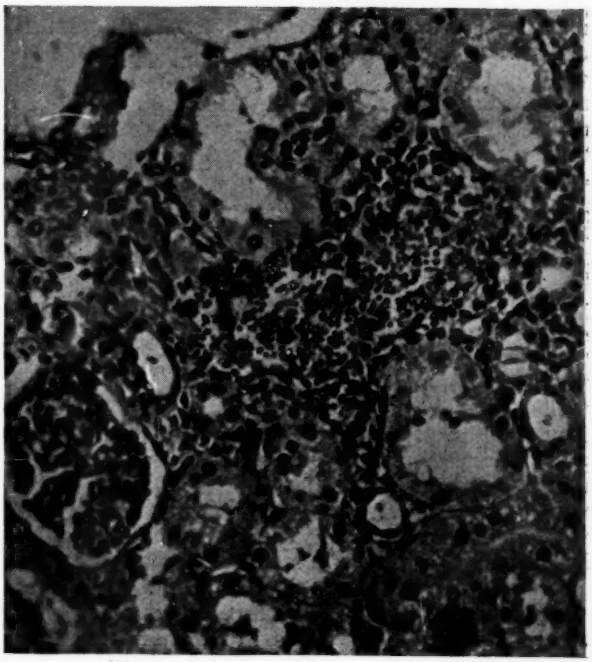

FIG. 5.—Thrush lesion of kidney (case 169). × 120.

in the literature is, however, small, and the majority of reported instances involve drug addicts in whom mycotic endocarditis was found at necropsy. In Wessler and Browne's case (1945) monilia albicans was isolated from blood cultures on five occasions in a patient suffering from acute tracheobronchitis. The same organism was isolated from faeces, urine, bronchial secretion, and the pharynx of the patient who recovered with sulphonamide treatment. Purpuric lesions in a case of monilaemia are mentioned by Wickler et al. (1943) but the authors indicate that these may have been caused by an overdose of paraldehyde. Case 72 of our series had a petechial rash during life and purpuric lesions were noted in the abdominal skin at necropsy. Morris et al. (1945) recorded a case of monilia meningitis in a man of twenty-three, in whom monilia albicans had been isolated from the pus in a tooth socket in the lower jaw. Miale (1943) reported one case of monilia meningitis in a man of thirty years who for eight years had been suffering from a monilial granulomatous lesion of mouth and tongue. Zimmerman et al. (1947) reported a case of monilia meningitis with recovery after an eight-day course of streptomycin.

Intestinal lesions. Paterson (1947) speaks of 'a tendency for the infection to "work through" the child so that it is accompanied by severe vomiting and diarrhoea and gives rise to grave general symptoms with blood in the stools.' Extensive haemorrhage into the lumen of the stomach was found in four of our cases and into the small gut

in two cases, but no attempts were made in these six cases to demonstrate the presence of monilia albicans by histological or bacteriological examination. In our series there was evidence of intestinal ulceration in four cases, but although similar in naked eye appearance, only one case was proved to be thrush by histological and bacteriological examination. In case 142 there was a greyish adherent membrane consisting of fibrin, sloughed-off mucosal cells, and masses of organisms. Monilia was not found either by histological or bacteriological examination. In case 206 small oblong punched-out areas of ulceration, surrounded by a haemorrhagic zone, were noted. Histological and bacteriological examination did not reveal monilia. In case 72 there was extensive emphysema of the wall of the ulcerated ileum, but thrush was not found. In case 169 a greyish pseudomembrane was present in the upper ileum, and in its lower parts there was extensive ulceration of the mucosa which was covered by yellowish adherent masses. Monilia was found in the section and on culture. The inflammatory reaction extended about 2 inches from the thrush ulcer (fig. 6). Macgregor and Henderson (1943) have described two cases with lesions half-way along the small intestine and above the ileocaecal valve respectively. Ebbs (1938) mentions extension to the intestines in two of his twenty-two cases.

Spread to tympanic cavities. The incidence of involvement of the tympanic cavities and mastoid air cells in the present series was high, as would be expected in infants with recurrent vomiting. In ten cases unilateral or bilateral otitis media was present. In four of these cases (Nos. 123, 190, 206, 212), monilia albicans was found either in smears or on culture; in four cases monilia could not be demonstrated and in two cases bacteriological examination was not carried out. Ebbs (1938) mentions two cases with otitis media, showing thrush spores in the discharge, and greyish pus and bone necrosis at necropsy.

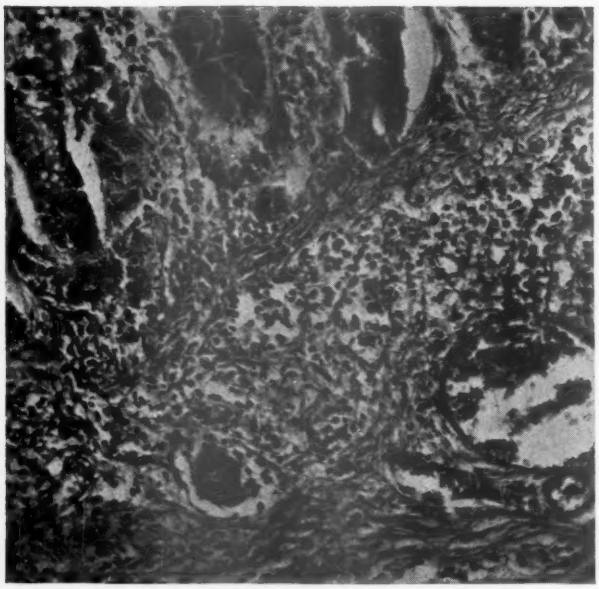

FIG. 6.—Inflammatory reaction in intestinal submucosa 2 in. from thrush ulcer (case 169). × 165.

Discussion

Thrush in infancy is so common that its occurrence is generally regarded as of minor importance, but histological examination of thrush lesions of the pharynx and oesophagus may reveal epithelial oedema, desquamation, hyperaemia, and infiltration which may extend into the surrounding tissues. The inflammatory process may spread by direct extension to involve neighbouring structures such as the pleura or diaphragm but dissemination through the blood stream may also occur.

Thrush may pass unrecognized at necropsy unless histological examination is undertaken, because of the lack of specific macroscopical features to suggest the diagnosis. A large variety of organisms may be isolated from swabs taken at necropsy from oesophageal and pharyngeal lesions. In our cases coagulase-positive staphylococcus aureus, non-haemolytic streptococci, enterococci, Bact. coli, proteus, and Pseudomonas pyocyanea were most commonly found. It is often difficult to resolve one's doubts as to whether one or more of these organisms are primarily responsible for the post-mortem appearances. There are two possibilities, either the thrush lesion is the primary one and this becomes secondarily invaded by other organisms, or other organisms produce the primary lesion which becomes secondarily infected with monilia. The morphology of the early lesion (fig. 1), however, would seem to favour the former view that the fungus by primarily damaging the epithelium provides a basis for invasion of the body by organisms normally present in the alimentary tract. In a control series of fifteen infants who died from a variety of causes but in whom the oesophagus looked normal, swabs were taken from the oesophagus and examined directly and also cultured. Monilia albicans was not seen on direct examination in any of these cases, although in two cases a positive culture was obtained on Sabouraud's medium; in addition the same types of organisms as were isolated in our thrush cases were found in these control cases. This suggests that the infiltrating fungus is responsible for the primary lesion and secondary infection occurs from organisms normally present in the oesophagus.

In six of our cases sudden death occurred as a result of blockage of the respiratory passages by food regurgitated from the stomach, and in eleven other cases there was histological evidence of inhalation of vomit. We consider that inhalation of gastric contents is one of the characteristic features of thrush in infancy. This occurrence may be due to interference with the normal act of

swallowing because of dysphagia caused by painful thrush lesions, or possibly the thrush pseudomembrane may make the protective pharyngeal reflexes insensitive. These reflexes may also be depressed in other conditions, such as prematurity, congenital malformations (for example, cleft palate), mental deficiency, cerebral haemorrhage, or in debilitated children and children under the influence of narcotics. Gardner (1942) considers that aspiration of vomit is almost exclusively limited to artificially fed babies. He observed that the stomachs of breast-fed babies were small and compact, whereas those of bottle-fed babies were often grossly distended as a result of air swallowed during feeds. He considers that attempts to expel this air lead to aspiration of vomit. White (1948) does not agree that aspiration of vomit is so rare in breast-fed babies, and in his series of twenty-three infants who died suddenly following aspiration of stomach contents, four of the twelve infants whose mode of feeding was known were breast-fed. In our series, three infants were breast-fed, none died from massive aspiration of gastric contents, but in two cases there was histological evidence of aspiration pneumonia. Rhaney and Macgregor (1948) found histological evidence of inhalation of gastric contents in forty-one newborn babies in a series of 939 necropsies. They considered that prematurity, cerebral haemorrhage, and poor general condition of the infant were predisposing factors. Only two of our cases were premature but in both aspiration of vomit had occurred; in none of our cases was cerebral haemorrhage present clinically or at necropsy; fourteen of our cases were dehydrated and in poor general health on admission to hospital.

Eight infants of this series were born within a period of four months in the same maternity unit. Two infants born on the same day died at the same age of twenty days, three infants born on three successive days died after twenty-nine, thirty-seven, and twenty-three days respectively. Although the number is small, it seems highly probable that the monilial infection was contracted in hospital. This infection appears to have been the cause of the fatal illness. The period of observation was too short to say whether the occurrence, within four months, of a large number of fatal thrush infection in neonates was due to seasonal conditions, to the spread of a particularly virulent strain of monilia albicans, or was purely accidental.

We are, because of the relatively small number of observations, not in a position to analyse the incidence of thrush infection in older infants and to state whether or not a thrush infection was primarily responsible for a period of ill health or whether the infection was established secondarily in an ill infant. Nevertheless, once established, the infection may represent a serious danger to the infant's life and all precautions should be taken to avoid infection and, when present, to avoid spread in and from the affected infant. Ludlam and Henderson (1942) and Anderson and her associates (1944) have investigated the source and spread of moniliasis and their recommendations should be applied.

Summary

In a series of 204 necropsies on infants under twelve months of age, twenty-six cases were encountered in which monilia infection was responsible either directly or indirectly for the fatal outcome. The danger of thrush infection to the infant, namely extension into the oesophagus with the subsequent syndrome of refusal of feeds, vomiting and dehydration, aspiration of vomit, septicaemia, intestinal spread, and monilaemia are described. Diagnostic difficulties in the living and at necropsy may be responsible for a significant number of cases of fatal thrush lesions which remain undetected and unrecorded.

We wish to express our thanks to Professor Norman B. Capon, A. W. Downie and H. L. Sheehan for their advice and criticism, and to Dr. W. E. Crosbie for access to the patients in Alder Hey Hospital.

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THE CHANGING INCIDENCE OF CONVULSIONS IN CHILDHOOD

BY

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Infantile convulsions have long been an enigma and in spite of the progress of medical science there remains much that is still not clear. Infants have convulsions more often than adults or older children and for this fact various explanations have been adduced. The doctrine of peripheral irritation whereby the immaturity of the infant's nervous system was held to result in convulsions on the slightest provocation was obviously unsatisfactory and led to the acceptance of a fantastic variety of stimuli to which a particular fit might be attributed. The analogy of the rigor was also inadequate. Rigors in adults are in fact comparatively rarely encountered outside malarious areas, and in any case infants are not themselves immune from them.

Tetany or spasmophilia has long been recognized as a cause of convulsions but there has been little unanimity on the extent to which infantile convulsions must be regarded as hypocalcaemic. In parenthesis it may be mentioned that with modern methods of estimating the blood calcium, the term 'hypocalcaemia' is to be preferred to either 'tetany' or 'spasmophilia' when discussing the etiology of convulsions. The lowering of the blood calcium is the only safe criterion for the diagnosis of the convulsions of tetany: other signs are very frequently absent.

Although Thiemich (1906), Husler (1920, 1921), and Zappert (1932) all recognized spasmophilia, which was quite distinct from epilepsy, as a cause of convulsions in infancy and early childhood, they also recognized a benign, non-recurrent 'casual' convulsion, first postulated by Hochsinger (1904) which was considered to be distinct both from tetany and epilepsy. Gebhardt (1914), however, considered most of these latter convulsions to be in fact spasmophilic. Husler and Spatz (1924) investigated the convulsions of whooping-cough and concluded that they were only very rarely spasmophilic in spite of the frequent association of rickets. Powers (1925) using the recently described micro-methods for the estimation of blood calcium, found on the other hand that most of the convulsions of whooping-cough were hypocalcaemic. The position was further complicated by the suggestion that tetany and epilepsy could not be separated so clearly and that the sequelae of recurrence and mental degeneration could follow upon tetany also (Collier, 1928; Kennedy, 1931; and Voigt, 1942).

Graham (1932, 1933) discussing convulsions in the first two years of life, showed that in Glasgow the commonest cause was hypocalcaemia. He had been struck by the number of children who had a convulsion at the onset of an acute infection and had also a demonstrable hypocalcaemia. If his views were correct then it would be reasonable to suppose that

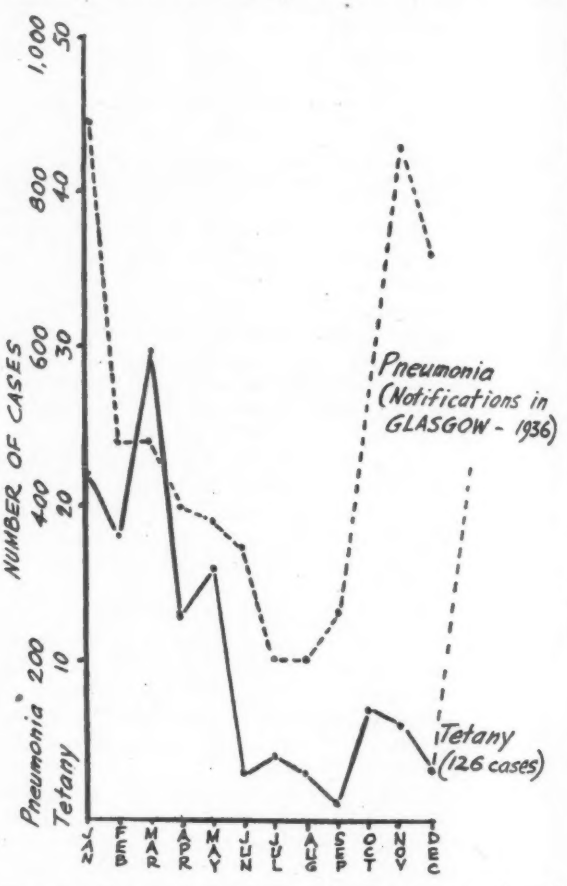

FIG. 1.—Seasonal incidence of tetany and of acute primary pneumonia.

these convulsions would show the same seasonal incidence as tetany. They would appear particularly in late winter with a peak incidence in the spring. On analysis of his cases this was found to be so, whereas a control series of convulsions associated with obvious intracranial disease showed no such seasonal variation. It was, therefore, unnecessary to postulate etiological factors other than hypocalcaemia, intracranial disease, and mental deficiency to explain infantile convulsions; epilepsy in the usually accepted sense of the term is not a diagnosis to be made at this age. In Sweden, Herlitz (1941) challenged these views in favour of a specific ' initial-fever convulsion ' distinct both from epilepsy and tetany. He particularly objected to the conclusion that the seasonal variation demonstrated by Graham was due to hypocalcaemia; he believed that it was no more than the seasonal variation of the associated diseases which were, in his cases, mainly acute infections of the respiratory tract. This argument seems to me to contain a false premiss. The seasonal incidence of acute respiratory infections in no way resembles that of tetany. If we take, for example, the notifications of acute primary pneumonia in Glasgow in 1936 and compare the curve (fig. 1) with that of tetany it will be seen that there is a pronounced time lag between the two curves and in particular the maximum for tetany occurs two months after that of pneumonia. Tetany gives a sharp peak in the spring (Thiemich, 1906, and Horstmann and Petersen, 1946) whereas pneumonia is obviously a disease of winter. It seems reasonable to suppose that the seasonal variation of other acute respiratory infections will follow that of pneumonia. In Ireland, Frazer (1944) sided with Graham in attributing to most infantile convulsions a rachitic basis. On the other hand Capper (1946) in America categorically denied that spasmophilia was anything but a rare cause of convulsions.

When discussing the incidence of rickets or tetany, locality and time are important and the divergence of opinion on the position of tetany as an etiological factor in infantile convulsions is most probably attributable in part at least to the different localities and periods studied. It is certain, for example, that Glasgow in the past saw very much more rickets and tetany than other cities with less poverty and over-crowding and more sunshine. Moreover, it is likely that Glasgow shared her unenviable reputation with Ireland rather than with Sweden.

It is common knowledge that there has been a marked fall in the incidence of rickets and tetany in the last decade or so and hypocalcaemia cannot to-day be regarded as a likely cause of infantile convulsions. It therefore seemed profitable to re-investigate the incidence of convulsions in order to confirm the seasonal variation of the past and determine any subsequent change. It was decided to investigate the incidence of convulsions for three representative quinquennia in the quarter century 1922-46.

Investigation

The periods chosen were 1922-26, 1932-36, and 1942-46. Records were available at the Royal Hospital for Sick Children, and the case-sheets of medical admissions were carefully scrutinized. All cases admitted with a history of convulsions or who developed one or more convulsions during the period of stay in hospital, were extracted. For the first period, when the medical wards of the hospital were undivided, all medical admissions were included; for the other two those of one medical unit only were taken. As the number of medical beds in the earlier period was less than in the later ones, there is no very great disparity. The total medical

TABLE 1

SEASONAL INCIDENCE OF CONVULSIONS IN CHILDREN UNDER THREE YEARS OF AGE NOT ASSOCIATED WITH PRIMARY DISEASE OF THE CENTRAL NERVOUS SYSTEM

	1942–46		1932–36		1922–26	
	Actual figures	Monthly admissions (%)	Actual figures	Monthly admissions (%)	Actual figures	Monthly admissions (%)
Jan. ..	15	2·8	19	6·4	29	5·1
Feb. ..	16	4·6	16	5·4	25	5·4
March ..	20	4·7	28	8·1	24	5·4
April ..	17	4·4	21	6·8	18	4·1
May ..	16	3·9	23	6·9	21	4·2
June ..	15	4·5	13	4·4	21	4·8
July ..	12	3·1	12	4·4	5	1·2
August ..	18	3·9	16	4·9	14	2·8
Sept. ..	20	4·5	15	4·6	15	2·8
Oct. ..	12	3·1	14	4·0	17	3·2
Nov. ..	14	3·5	12	3·8	16	3·6
Dec. ..	17	4·8	14	4·6	12	2·8
Total ..	192	3·9	203	5·4	217	3·8

admissions for the three periods under consideration were 5,706, 3,769, and 4,884.

For the purposes of the present paper only those cases not obviously associated with intracranial disease are included; we may also, as we are concerned only with infantile tetany, restrict our consideration to those under the age of three years. It is only necessary for our purpose to record the seasonal and age incidence of these cases, but it is worthy of mention that the striking fall in the number of cases with clinical evidence of rickets and tetany abundantly confirmed our clinical impression of the virtual disappearance of these conditions. Moreover, it is interesting to note that this fall became evident in the middle period before the war-time free issue of vitamin supplements and the fortification of dried milk with calciferol.

The statistical significance of these results is discussed in an appendix to this paper. It is interesting to note that 1932-36 shows a rather smaller seasonal variation than 1922-26 and that this is in conformity with the observations upon the fall in the incidence of rickets and tetany where it was found that a slow fall was already apparent in the thirties leading to an almost complete disappearance in the forties.

During the three periods there have been 126 cases of unequivocal tetany and the seasonal variation of these may be taken as typical. On comparison of this curve (fig. 1) with those of 1922-26 and 1932-36 the similarity is obvious. (In 1922-26 the curve for the actual figures does not show a peak in March: this is because the admissions in January, 1922-26, were unusually high. Otherwise the monthly

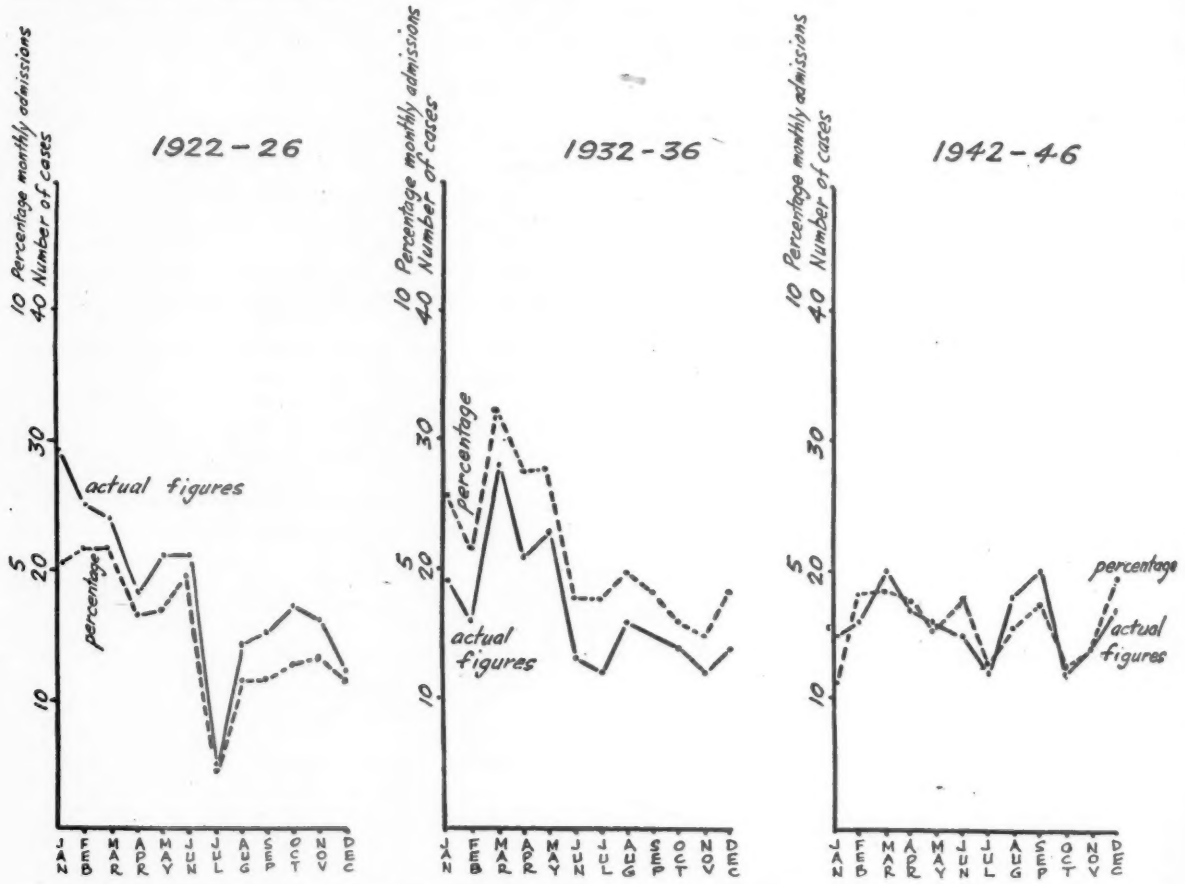

FIG. 2.—Monthly incidence of cases of convulsions under the age of three years, not associated with primary disease of the central nervous system.

Seasonal incidence. Table 1 shows the monthly incidence of these cases but they are better demonstrated graphically (fig. 2). The most striking feature of the three curves is the difference between that of 1942-46 and those for 1922-26 and 1932-36. The earlier curves fully confirm the seasonal incidence and the last shows its virtual disappearance. variation of total admissions has little effect on the seasonal variation as shown by the actual figures.)

Age incidence. The age incidence shows a similar alteration in pattern. It is only necessary to compare the findings of 1922-26 with those of 1942-46 (fig. 3) to demonstrate the striking fall in

the tetany age-group of six to eighteen months. There has always been a numerical preponderance in the first six months of life but formerly the tetany age-group was prominently represented. Again the middle period shows a position intermediate between however, much the same distribution. Thiemich's (1906) curve is substantially the same. There seems to be no reasonable doubt that the curve of incidence of convulsions during the two periods 1922-26 and 1932-36 is due to an associated hypocalcaemia.

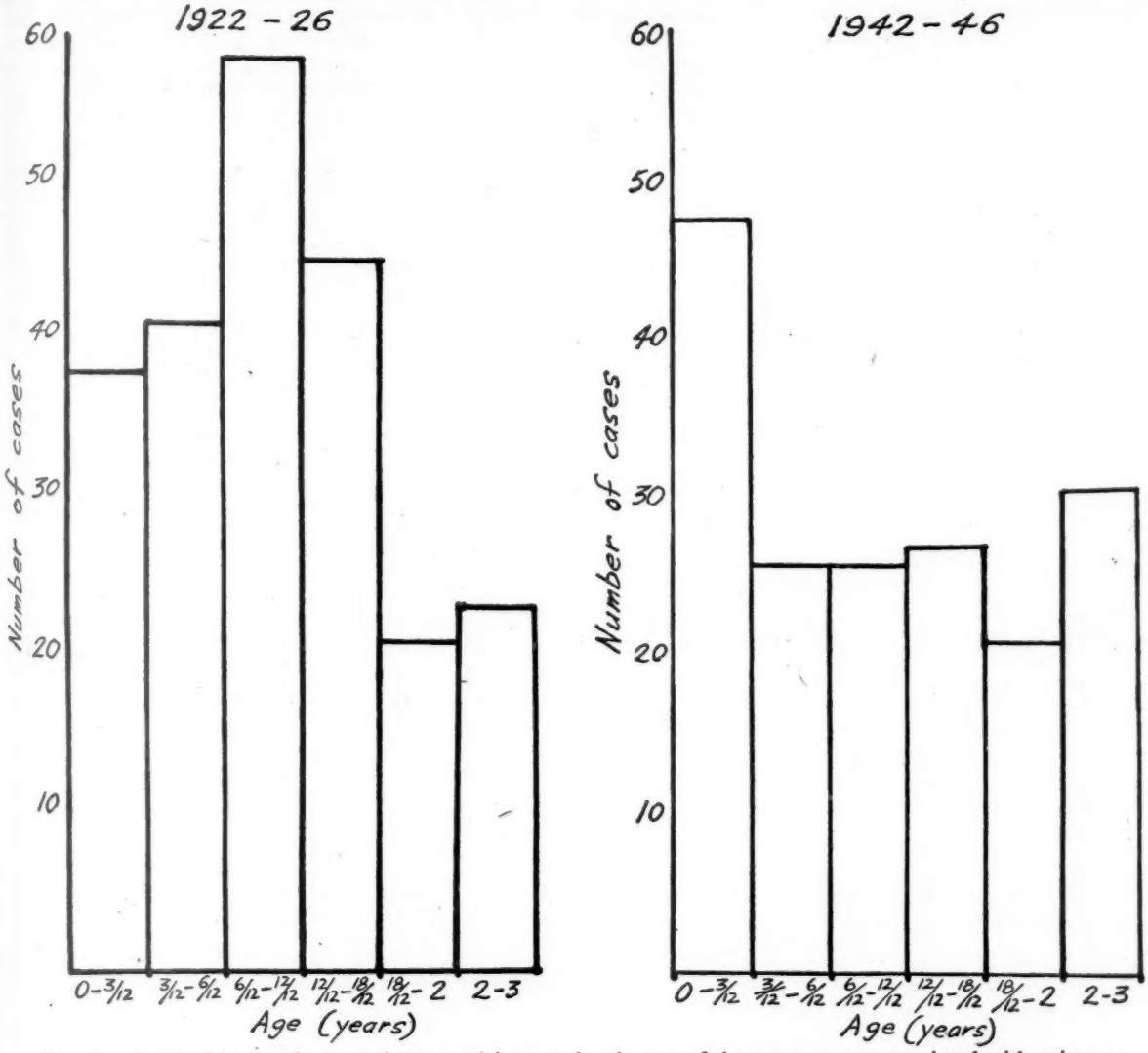

FIG. 3.—Age incidence of cases with convulsions under the age of three years not associated with primary disease of the central nervous system.

the two others. To-day the first three months are by far the most frequent age for the convulsions of infancy to appear. The 'teething' convulsions, therefore, have disappeared with the disappearance of tetany.

Discussion

The seasonal incidence of tetany is quite characteristic. Horstmann and Petersen (1946) make the point that the curve for tetany differs from that for rickets. In tetany there is a sharp peak in March whereas that for rickets is a rounder curve with, The peak in March and the trough in the summer and autumn is typical, and, moreover, it is very difficult to suggest why this seasonal variation should have disappeared if it is not due to the disappearance of tetany. This disappearance of the seasonal variation suggests that it is concerned with some factor that has radically changed in the last quarter-century. There has been no change in the actual incidence of respiratory infections whatever improvements there may have been in the therapeutics of these diseases. The notifications, for

example, of acute primary pneumonia in Glasgow have shown no significant fall since 1922 (M.O.H. Reports, 1922-1946).

We can hardly escape the conclusion, therefore, that there has been a striking alteration in the pattern of incidence of infantile convulsions in the last twenty-five years and that this has every appearance of being due to the virtual disappearance of hypocalcaemia as an etiological factor. That this was not so in other parts of the world is not only possible but likely. In the past the incidence of rickets in Glasgow was unusually high.

There is a corollary arising out of these observations that opens a wider field of speculation. We have seen that there has been a considerable fall in what has been the main etiological factor in the convulsions of infancy and childhood. Normally one would expect there to be a corresponding fall in the total incidence but this is not in fact the case.

Table 2 summarizes the general incidence of all cases of convulsions admitted during the three periods under consideration. The fluctuation of the total admissions with convulsions is not helpful but if they are expressed as a percentage of the total medical admissions a comparison is permissible. It becomes apparent that the number of cases with convulsions expressed in this way is the same for 1922-26 as it is for 1942-46. Not only are the totals unchanged but the relative numbers apportioned between primary disease of the central nervous system and the others has also remained the same. Table 1 shows a similar position.

General incidence of convulsions. How far it is justifiable to draw general conclusions on incidence from the numbers of admissions to hospital is, of course, problematical. In this instance, however, the figures are strongly suggestive; especially as it is possible to argue that these figures indicate that

TABLE 2

GENERAL INCIDENCE OF CONVULSIONS

	1922-26	1932-36	1942-46
Total admissions	5,706	3,769	4,884
Total number of cases ..	454	382	389
Percentage of total admissions	7·9	10·1	7·9
Primary disease of central nervous system as percentage of total cases	45·2	40·6	45·2

not only has there been no fall in the incidence of convulsions but that there has actually been an increase. The figures for the last two periods represent only the admissions to one medical unit. The total figures will therefore be about double this. It could be argued that there will be a tendency to admit an acute emergency such as a convulsion no matter what may be the state of the beds and that an increase in accommodation will result in a disproportionate increase in relatively minor cases. From this it would follow that the absolute increase in the number of admissions with convulsions would indicate an absolute increase in the incidence in spite of a relatively constant proportional incidence. However that may be, there has manifestly been no decrease in the incidence and this accords well with the findings in other parts of the world.

Summary and Conclusions

The seasonal and age incidence of convulsions in children under three years of age have been investigated for three five-year periods, 1922-26, 1932-36, and 1942-46.

The results demonstrate the characteristic curves of tetany in the first two periods with their virtual disappearance in the last.

From this it is concluded that in Glasgow hypocalcaemia was the predominant etiological factor in convulsions in the earlier periods under investigation but is so no longer.

The total and relative incidence of convulsions in infancy and childhood has not been reduced by this fall in the incidence of hypocalcaemia.

This investigation is in many ways a continuation of the work on convulsions by Professor Stanley G. Graham to whom I am grateful for suggesting the topic and also for ever present encouragement and unstinted advice. Dr. Robb's contribution is greater than the modest dimensions of his comment would suggest. I should also like to thank Dr. D. Campbell Suttie and his staff for access to records.

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STATISTICAL NOTE ON THE SEASONAL VARIATIONS OF TABLE I

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Table 1 gives the actual number of cases of convulsions in three five-yearly periods, 1922-26, 1932-36, and 1942-46. These numbers will not show the true seasonal effect owing to the fact that the number of days in each month is unequal. Over the five-year period 1922-26, for example, there are 165 days in January in which cases of convulsions can be admitted to hospital, but only 141 days for February, allowing one extra day for a leap year. The data of table 1 have, therefore, to be adjusted, and this has been done on the basis of 165 days for each of the calendar months. Table 1a gives the adjusted data.

TABLE 1a
ACTUAL INCIDENCE OF CONVULSIONS

	1922-26	1932-36	1942-46
Jan.	29	19	15
Feb. ..	29	19	19
March ..	24	28	20
April ..	20	23	19
May ..	21	23	16
June ..	23	14	16
July	5	12	12
Aug. ..	14	16	18
Sept. ..	16	16	22
Oct. ..	17	14	12
Nov. ..	18	13	15
Dec. ..	12	14	17
Total ..	228	211	201

The probability or chance of incidence of convulsions in any one month is very small, and the counts in any one month can be considered as distributed in the Poisson fashion. To test the hypothesis that in any five-year period the number of cases of convulsions in any one month is the same except for random or accidental variations, the Poisson index of dispersion, χ^2, may be used. If $\chi^2 > 19 \cdot 7$ we may say on the 5 per cent. level of significance that the hypothesis should be rejected: that is, a significant seasonal variation exists. The following results were obtained:

Period	χ^2	Remarks
1922–26 ..	28·1	Highly significant
1932–36 ..	14·8	Rather below significance
1942–46 ..	5·8	Not significant

Thus there is a significant seasonal variation in 1922-26 and a tendency to such during 1932-36. The figures for 1942-46 show, however, that if a seasonal variation exists it is obscured by the accidental variations.

CONGENITAL MALFORMATIONS IN ONE OF MONOZYGOTIC TWINS

BY

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The purpose of this communication is to describe two cases of gross foetal abnormality and to discuss the influence of intra-uterine environment on the development of congenital abnormalities when the contribution of inherited or genetic factors is made known by the co-existence of a genetically similar but normal twin. The anomalies will not be discussed in detail, but some explanation of the mechanism of their occurrence will be attempted, since, even if this proves incorrect, it may stimulate useful reconsideration of the problems presented by congenital malformations which now assume such a great importance in practice.

Like Twins and Factors Influencing Inheritance

If the outcome of intra-uterine development is determined solely by genetic inheritance, monozygotic or like twins should be completely indistinguishable from one another at birth. Right and left asymmetry with a mirror image difference often does exist, but this is not a valid difference and need not be discussed now. It is widely admitted, however, that even like twins may differ in size at birth. Moreover, Schatz (quoted by Newman, Freeman, and Holzinger, 1937) found that at about the middle period of pregnancy the size difference in monozygotic twins was greater than at term and, on the average, much greater than for dizygotic or unlike twins. The careful survey of the literature on twin pregnancies with one twin blighted made by Kindred (1944) is also relevant. Here one twin dies, usually between the third and the fifth month, and is retained in utero until the birth of its living partner at, or near, term. This condition has a roughly similar incidence in both monozygotic and dizygotic twins. The occurrence of this condition must suggest that the development of twins, even when they are derived from the division of the same fertilized ovum and possess an identical genetic inheritance, can be very significantly influenced by differences in the environment they establish for themselves in the maternal uterus. Joined or Siamese twins and double monsters are often closely identical (Szendi, 1939). Parasitic twins and teratomata, if it is insisted that these latter arise from cells laid aside so early in development, are both examples of much greater inequality of growth and even of organ differentiation. Here, however, division of the initial cell mass between the two individuals is relatively late, and may be unequal, and the juxtaposition of the growing tissues and the organizers of the two individuals may disturb development. These more extreme abnormalities are, therefore, unsuitable material for a study on genetically similar material of the role of environmental differences in utero and especially for the study of the effect of nutritional differences.

Despite the value of the study of like and unlike twins in the assessment of the relative contribution of the environment and of heredity in post-natal life in health (Newman, Freeman, and Holzinger, 1937, and Newman, 1942) and in disease (Kallmann and Reisner, 1943), twins have been little studied for data on the relative importance of environment and heredity in intra-uterine development. The Mateer embryo of the pre-somite period (Streeter, 1920) showed a normal embryo and probably also an abnormal and yet monozygotic twin. Such cases are of interest, but have not been discussed in this connexion. Macklin (1936) collected from the literature cases of malformation in twins. The records rarely indicated the nature of these twins. She found, however, that twins of like sex were concentrated in the group where both twins were malformed. Where but one twin was malformed, the twins were presumably binovular (dizygotic), because they were as often of different sex as ordinary siblings. She argued that this was good evidence that malformations were not determined by environmental causes, but were due to inherited defects of the genetic inheritance. To-day there is convincing evidence that some congenital malformations can, and do, arise from environmental causes, such as rubella. It is not necessary to think that even identical abnormalities always have the same causes. Environmental causes may create copies (phenocopies) of conditions which are more often determined by genetic factors (Goldschmidt, 1938). Information on any environmental conditions which may operate in this way is most desirable.

The probable nature of this environmental disturbance must be considered. Studies of the occurrence of malformation when the maternal diet is deficient, and where it is presumed in consequence that embryonic nutrition is also deficient, provide some evidence in animals, but no satisfactory

evidence that in man nutritional requirements can determine malformations. The blighting or death of one ovum of a monozygotic pregnancy is probably to be regarded as the result of unequal sharing of nutrient. The deficiency usually leads to death and, if abnormalities are present in the dead and blighted ovum, it will very likely be impossible to establish this months later from its macerated or papyraceous remains. The uterus otherwise must present a very similar environment to both twins and such maternal influences as general nutrition, infection, and toxaemia should affect two genetically similar embryos equally.

Criteria for Diagnosis of Monozygotic Twins

It is necessary to decide on what basis a diagnosis of monozygotic or like twins can be made. Diagnosis by the study of the foetal membranes has fallen into some disrepute among those who study twins in late post-natal life. A casual examination of these membranes is useless and they must be properly examined grossly and microscopically and with adequate tissue sections. Very rarely monozygotic twins are enclosed in a common amnion; usually they are separated only by the walls of their amniotic cavities and the chorion should continue as a common membrane around both. In dizygotic twins there are four membranes between the foetuses, two amniotic and two chorionic layers (dichorionic placentae), and, though the two placentae may appear fused, there is no continuous layer of chorion from one placenta to the other. Some confusion has been caused because some workers have failed to recognize that a fairly high proportion, probably about 30 per cent., of monozygotic or like twins are born in dichorial placentae. In these cases the ovum cleavage has occurred early; the separated cells are not enclosed in a common membrane and each forms its own chorion.

It is important to decide if dichorionic, usually dizygotic, twins can come to possess a single chorion. Arey (1922) has suggested on insufficient evidence that occasionally the two separate chorionic cavities may become continuous with one another through the breakdown of the adjacent chorionic walls. If this occurs the retention of a partition formed by two thin and fused amniotic walls would seem somewhat unlikely and such twins would probably be described as monochorionic twins with a common amnion. It is highly improbable that those monozygotic twins of identical inheritance who possess a monochorionic placenta and two amnions will be mistaken for dizygotic twins of unlike inheritance, if the membranes are carefully studied. Additional support for a monozygotic origin may be provided by a study of the placental blood vessels. There is some agreement that in man readily demonstrable blood vessel anastomoses are associated only with monozygotic twins. Thus von Verschuer (1939) injected placentae and found thirty-two cases with circulatory anastomoses and these were all monozygotic twins on complete tests of resemblance. In one hundred cases there were two chorions and no anastomoses, and of these seventy-six were dizygotic and twenty-four were monozygotic after similar studies. It would seem that only some monozygotic twins possess such anastomoses and that in man, as opposed to cattle, unlike twins do not mix their blood.

The only alternative to such a study of foetal membranes is a meticulous comparison of blood groups, eye colour, iris pattern, hair and skin colour, form and texture, finger and palm prints, and general features. This is largely impossible in malformed infants, one or both of whom may die at birth. It prejudges the issue since only if there is close physical correlation will the diagnosis of monozygotic twinning be made. It was not employed in the cases to be described. Blood grouping is difficult in the newborn and could scarcely be useful when there are communications between the circulation of the two twins. Some comparisons might, however, give useful collaborative evidence of genetic identity in future cases.

Case 1. Mrs. A, a primipara aged 45 years, was admitted at twenty-five weeks with severe pre-eclamptic toxaemia, oedema, urine loaded with albumen, and a blood pressure of 160/80. At thirty weeks spontaneous labour occurred and two stillborn female infants were delivered.

The placentae were fused, the partitions between the foetuses had been accidently torn in some places, but multiple sections of this and of the junction between the placentae of each foetus showed only amnion in the partition and the chorionic membrane was continuous from one placenta to the other. Several large blood channels (fig. 1) passed

FIG. 1.—The circulations of the twins communicate by blood vessels, one of which is clearly seen. (Case 1.)

from the circulation of one foetus to the other.

FOETUS B. Intrapartum stillbirth. There was a history of maternal toxaemia, breech presentation, prolapse of the cord through the incompletely dilated os, and cessation of cord pulsation during attempts at replacement. In the foetus there was asphyxial petechial haemorrhage in the heart, lungs, thymus, and subserosal tissues, and gross congestion of all organs.

Prematurity was 30 weeks; weight 1,800 g. Crown to heel measurement, 41 cm. There was evidence of early intra-uterine maceration.

FOETUS C. Intrapartum stillbirth. The congenital anomalies of the heart were persistent ostium atrio-ventriculare communis, with an incomplete septum primum and absence of the septum secundum, a single atrio-ventricular valve, and an incomplete interventricular septum; dextro-position of the aorta; hypoplasia of left ventricle; and slight coarctation of aorta (infantile type). There was congenital atresia of the oesophagus without tracheo-oesophageal communication (variant of Type I of Ladd, 1944). There was gross dilation of the vagina and dilation of the cervical canal and corpus uteri with a shelf-like diaphragm at the lower end of the vagina (fig. 2) and retrograde leakage of vaginal squamous epithelial debris into the peritoneal sac with extensive vernix peritonitis (fig. 3). Prematurity

FIG. 2.—The large vagina, the dilated endocervical canal and uterus, and the complex shelf-like folds in the lower vagina which constituted the only obstruction, are shown. (Case 1, Foetus C.)

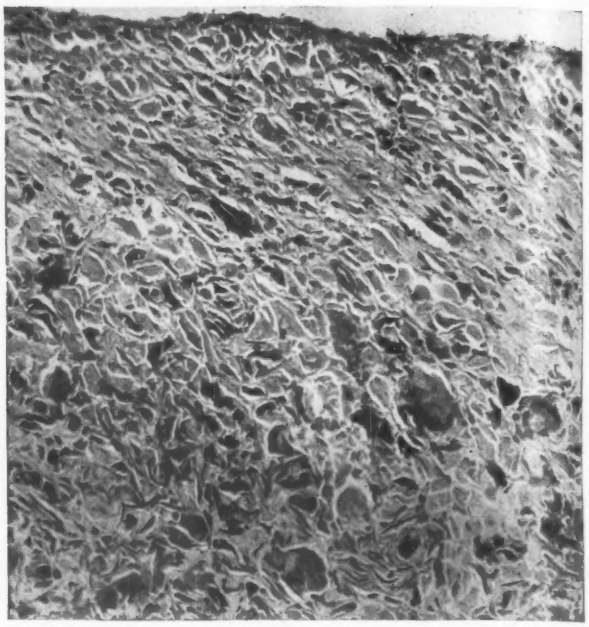

FIG. 3.—Vernix squames have stimulated some peritoneal reaction by mononuclear cells and by multinucleated giant cells. (Case 1, Foetus C.)

30 weeks; weight 800 g. The crown to heel measurement was 33 cm.

In foetus C the cardiac anomalies are those which would arise from disturbances of those growth processes which are normally most active at the end of the fifth and beginning of the sixth week of embryonic life. The anlage of the septum primum has then appeared, the antero-superior and postero-inferior endocardial cushions between the future auricles and ventricles are present, the interventricular septum is incomplete, and the spiral subendocardial bulbar ridges have formed but have separated the aortic and pulmonary channels only in the distal part of the bulbus. The actively growing free edges of the septum primum have not united with the endocardial cushions, nor have these fused to divide the single atrioventricular channel into right and left channels. The interventricular septum is growing upwards, but will not complete the separation of the ventricles until about the eighth week. The growth of the bulbar ridges is active, but not complete, in the proximal portion of the bulbus, and the positioning of the aortic and pulmonary orifices is therefore not determined. Most of these changes will occur in a few days and, whatever might subsequently happen, the heart found in this foetus could not then be produced. In the fifth and sixth weeks there is an almost solid mass of epithelial cells representing the future lining of the oesophagus. These cells must multiply rapidly at this time as the oesophagus is drawn out by the rapid growth of this region with the development of the heart and lungs. Disturbed or incoordinated

growth may interrupt the continuity of the epithelium and stenosis or atresia may result. The uterine anomaly is unusual. It can perhaps be regarded as a disturbance of the lower end of the Mullerian duct system. It is difficult to explain its formation at any stage of development. In the sixth week the right and left paramesonephric ducts have appeared in the mesenchyme lateral to the cranial extremities of the mesonephric ducts. They are growing downwards and in each a lumen is extending towards the growing tip. Disturbance of growth activity at the lower end of these ducts may create abnormalities which later affect their complex development even after fusion. There are many other active growth changes occurring at this period. The future ureter and pelvis is growing upwards and the primordia of the metanephros is appearing. The kidneys and ureters in this case were not affected but the critical growth period for these and other structures is uncertain. The urorectal septum may not have completed the separation of the rectum and urogenital sinus, but here growth activity at this period is relatively slight.

Case 2. Mrs. X was a primigravida aged 23 years. She had mitral stenosis. Twins were not expected but at thirty-five weeks gestation she was delivered first of a normal live female child and this was followed by a dead-born monster.

The placentae were complete. There were two amniotic cavities enclosed in a single chorion, and the relationship of the membranes was confirmed by histological examination. The umbilical cords arose within 1½ in. of each other. Large communicating channels passed between the arteries of each twin and between the veins.

Child Y is alive and well and shows no congenital defect.

FOETUS Z. Intrapartum stillbirth. There was occipital encephalocoele, complete spina bifida, Arnold-Chiari malformation; gross dysgenesis of the larynx, complete atresia of the trachea and oesophagus, and isolated lung rudiment; cor biloculare with imperfect incorporation of the sinus venosus and bulbus cordis, and diffuse endocardial fibro-elastic thickening. Scoliosis and kyphosis and imperfect development of all limbs was noted. There was gross dysgenesis and extreme hypoplasia of the liver, no recognizable stomach dilatation or pancreatic outgrowth, also absence of the urorectal septum and an imperforate anal membrane. There was a single hydronephrotic kidney with imperforate ureter, and ovaries without a demonstrable duct system.

The lungs were represented by a nodule of tissue 2 mm. in diameter in the neck, and recognizable only by histological examination. No trachea or oesophagus could be found and the larynx was a flat groove in the floor of the pharynx with two cartilage plates lying in front of this. An ovary was identified histologically.

The disturbance of development affected almost every structure, and the primary disturbance may well have been one operating for a period about the fourth week of intra-uterine life. About this period embryonic growth activity, which is slightly more advanced in the head region, is directed to the closure of the neural groove in the region of the spinal cord and to the organization of the overlying mesoderm. The primitive pharynx is forming and the laryngo-tracheal groove on its floor is the site of active growth which will later form the trachea and the paired lung buds. The four divisions of the heart are present and still separate (sinus venosus, atrium, ventricle, and bulbus cordis), but soon the septum primum and the bulbar ridges are to appear and the heart should assume its more adult shape and the auricular and ventricular chambers be divided by their septa. The differentiation of the skeleton of the limb buds is at a critical stage. The anlage of the liver has appeared but the stomach enlargement and the dorsal and ventral outgrowths of the pancreas are scarcely to be recognized. The expanding cloaca has scarcely yet begun to be divided by the growth of the urorectal septum. Development of a part of the genito-urinary system is also active, but even if this were disturbed, renal structures might still be derived at a later date from the caudal end of the Wolffian duct system where developmental activity is somewhat later.

Suggested Mechanism for Production of Abnormalities

In both cases multiple sections of the partition between the foetuses showed no extension of chorion into the partition between the two foetuses. Both, and especially case 2, showed anastomoses of large blood vessels of the two circulations. In neither case was one foetus parasitic on the other. Competition between the circulations of two foetuses for the utero-placental site is likely to be keenest in the early growth period when villi are growing out from the entire surface of the chorion. Later, when the site of villous attachment normally comes to cover only a part of the larger chorion, there is a more ample area for each circulation to develop in some independence from the other and from localized defects in the maternal decidua.

It is perhaps reasonable to suggest that one twin in both of these pregnancies experienced inadequate nutrition early in gestation, but, unlike most blighted ova, survived to experience an ample nutrition which permitted continued growth as gestation continued. Any extraneous influence, such as maternal toxaemia or infection, should have affected genetically equal twins equally. This deficiency of nutrition is not likely to have been a complete deprivation of one or more specific substances, though those substances whose transfer at that period of gestation was most difficult would be most seriously reduced. It is most useful to regard the disturbance as a somewhat non-specific influence causing an 'arrest of development.' Ingalls (1947) and Ingalls and Gordon (1947) have elaborated the earlier work of Stockard on

non-mammalian embryos and have suggested that development can be arrested in a variety of ways and that the result is not specific to the agent, but depends on the time of development at which the agent acts. The disturbance operates not on some specific organ or stage of differentiation, but on whatever organ or organs happen to be undergoing the most active growth changes at that time.

A profound knowledge of normal development might enable the time of a developmental arrest to be established and perhaps related sometimes to the operation of a known agent such as German measles. Developmental changes are crowded together, especially in the second month, but, if the arrest of development has affected several organs whose development has been at a recognizable stage, the coincidental occurrence of abnormalities in different organs might be significant and suggest a non-specific environmental agent operating at a period critical for the development of all of them. A disturbance in growth activity and in the production of those chemical substances which are concerned with organ differentiation will cause retardation and disorganization in those organs which are at that moment developing most actively. Other parts of the body, which are also growing, but at a slower rate, and whose demands are less exacting, may be less disturbed. When conditions improve these may continue their growth with little disturbance and establish their normal connexions. A stage of development once omitted cannot take place at a later period, but its omission may disturb development at a later stage or in another organ. Embryological data are much concerned with when developmental processes start and finish, but neither of these events may be of essential importance and data on the critical periods of growth in different organs are most desirable. There are many difficulties in the detailed study of multiple congenital anomalies, and embryology has contributed little to an understanding of the mechanism of their occurrence. The coincidence in different organ systems of what may be regarded as arrests of development is often surprising in cases, such as those presented, where there are multiple abnormalities. Especially when the genetic contribution is revealed by the existence of a monozygotic and normal twin, this seems to favour an environmental causation as opposed to a genetic basis.

Though these two cases are presented to suggest that environment sometimes determines congenital malformation, it is not intended to suggest that the environment is the only cause of congenital malformation. If this viewpoint should receive further support efforts to improve the supply of the metabolic constituent or constituents limiting embryonic growth at the critical period, perhaps by increasing the level in the maternal blood, are relevant and might result in some reduction in the incidence of congenital malformation. A belief in the exclusive operation of an unalterable genetic inheritance must be avoided.

Summary

Two sets of twins with monochorionic placentae and placental vessel anastomoses are regarded as monozygotic twins. One of each set showed malformations affecting many different organs. Since the genetic inheritance of the malformed twin should be similar to that of its normal partner, it is suggested that the malformations arose from an arrest of normal development when the placenta of one twin was at some environmental disadvantage in obtaining nutrition from the utero-placental site for a short period early in intra-uterine life. The abnormalities found were consistent with some such non-specific influence causing an arrest of development of those structures whose formation might be in a critical stage at about the sixth and fourth week respectively.

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FAMILIAL CONGENITAL STRIDOR

BY

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Almost a century has passed since Rilliet in 1851 described a case of stridor occurring in a young infant. This he presumed to be due to compression on the trachea by either a thyroid or thymic swelling. In 1853 Rilliet and Barthez in their classic French textbook on diseases of children were the first to describe as a clinical entity the condition which later came to be known as congenital laryngeal stridor.

Thirty years later Lees (1883) in Great Britain gave a description of a case of ' a peculiar form of obstructed inspiration,' in which examination by a laryngoscopic mirror previously had shown the aryteno-epiglottic folds to be close together and almost overlapping. Because the child had died of diphtheria, the larynx was examined post mortem. Lees claimed to be the first to describe the laryngoscopic appearances and post-mortem findings of such a case, and he stated that he had seen clinically a total of four cases with a similar condition. In the following year Gee (1884) described several instances of ' respiratory croaking of babies,' and made the observation that the disorder caused more annoyance to others than to the child.

The description of ' infantile respiratory spasm ' by John Thomson in 1892 helped to separate out a large group of cases of laryngeal stridor in young infants which ran a benign and self-limiting course.

In 1897 Sutherland and Lambert Lack described eighteen cases of ' congenital laryngeal obstruction,' of which six had been examined by a laryngeal mirror. In all of these, they noted the epiglottis sharply folded on itself, the two lateral folds being in close apposition. The aryteno-epiglottic folds were approximated, and thus the upper aperture of the larynx was reduced to a long narrow slit. The thin folds bounding the aperture ' flapped to and fro ' on respiration. They were convinced that there was a valvular action of the upper aperture of the larynx, dependent partly on a peculiar congenital malformation in the anatomy of the larynx and partly on the flaccidity of these parts in infants. This is the view that is now widely held.

In collaboration with Logan Turner, Thomson presented a comprehensive description of this group in 1900. They described the classical picture of the child who developed noisy breathing shortly after birth. The stridor comprised a croaking sound which accompanied inspiration. Expiration was accompanied by a short croak when the stridor was loud, but at other times it was noiseless. There was no distress and no cyanosis. There was marked inspiratory indrawing of the thoracic and abdominal walls, except in the mildest cases. During the first few months of life the stridor increased in loudness as the child got stronger, but after remaining about the same for a few more months, it gradually lessened and disappeared during the course of the second year. Structurally there was an exaggeration of the peculiarities of the infantile larynx. They postulated an ill-coordinated, spasmodic action of the muscles of respiration as the primary cause, and the soft collapsible nature of the larynx as playing only a secondary part in the condition. They considered that the peculiar laryngeal deformity was thus purely an acquired one as the result of a nervous imbalance. While this view has not now many followers, Thomson's (1892) original clinical description of the condition could hardly be improved upon. Reardon (1907) reviewed the already fast growing literature on the subject. Thereafter the increasing use of direct laryngoscopy led to more accurate diagnosis in cases of infantile laryngeal stridor.

M'Kenzie (1925) described a case of severe congenital laryngeal stridor with dysphagia, aged three years, on whom a tracheotomy had to be performed, and he gave a critical review of the theories of the etiology of supra-glottic stridor. He reported observations made by Paterson using direct laryngoscopy. When Paterson held one side of the sucked-in margin of the laryngeal orifice with forceps, the noise stopped at once.

Although Variot had, a generation previously, suggested cutting away the aryepiglottic folds, Iglauer (1922) was apparently the first to undertake partial epiglottidectomy in a case of congenital laryngeal stridor, and he advocated this procedure in all such cases subject to asphyxial attacks.

Schwartz (1944) claimed to have taken the first coloured motion picture of the larynx during respiration in a case of congenital laryngeal stridor, and reproduced in his paper striking photographs from the film. He suggested the adoption of the term ' inspiratory laryngeal collapse,' and stressed the role of micrognathia as an etiological factor in these cases. He showed how the muscular and ligamentous forces concerned in the upper aperture of the larynx were affected by micrognathia. He

carried out partial epiglottidectomy in one of his cases with relief of symptoms. One of his cases with both micrognathia and inspiratory laryngeal stridor had a brother also presenting both features.

Enlargement of the thymus is frequently stated to be an important cause of stridor in infancy. Kennedy and New (1931) reported from the Mayo Clinic a group of cases of chronic stridor in childhood. In fifteen of these cases, stridor was the chief complaint, but nine of these had been previously diagnosed as being due to thymic enlargement: eight out of nine had received x-ray treatment without benefit. Publishing a short series of illustrative cases, Trimby (1943) also has shown how rarely simple thymic enlargement is responsible for stridor or respiratory embarrassment in infancy.

The series of Bowman and Jackson (1939) of thirty consecutive infants, seen over a five-year period with chronic stridorous breathing, is of particular interest. Some degree of thymic enlargement was reported radiologically in twenty-one of these cases, but after careful investigation including x-ray examination, direct laryngoscopy, and bronchoscopy, the following diagnoses were made:

TABLE

No. of Cases	Diagnosis
14	Supraglottic obstruction to inspiration due to deformity or flaccidity of the epiglottis, arytenoids, and/or aryepiglottic folds
5	Enlarged thymus causing pressure on the trachea
2	Hypertrophic laryngitis
1	Web-like ridges in the subglottic area
1	Thickening of one of the ventricular bands
1	Congenitally small larynx
1	Cyst of thyroglossal duct with pressure of the tumour from the base of the tongue upon the larynx
1	Tuberculous bronchial lymph glands
1	Micrognathia
1	Collapse of part of the trachea
1	Congenital heart disease
1	Cause not found

This last series gives a rough idea of the relative frequency of the causes of chronic stridor in early infancy, and it emphasizes the need for routine chest x-ray investigation and direct laryngoscopy in all such cases. Thus approximately half the cases of chronic stridor encountered in infancy are due to 'inspiratory laryngeal collapse.'

There are many types of structural congenital anomalies of the larynx associated with stridor. Apart from the inspiratory collapse group, the most common of these is the presence of a membranous web joining the anterior ends of the vocal cords. A stenosis of the larynx as a whole is occasionally met, while cysts, haemangiomata, or papillomata are sometimes found to be the cause of the stridor, especially in older children. It is thus now becoming increasingly recognized that the term congenital laryngeal stridor embraces a considerable number of separate conditions.

The occurrence of three cases of laryngeal stridor in one family is considered to be of sufficient interest to warrant their publication. There have been four children in this family, all girls. All but one have been similarly affected with laryngeal stridor, and all those affected died.

A careful inquiry into the family pedigree on both the father's and the mother's side was made. There was no apparent consanguinity of the parents. The father, who was healthy, was an only child, but his parents were both from fairly large families. The mother, who suffered from bronchitis, was one of a large family, several of whom had children of their own. There was no traceable family history of 'throat trouble in infancy.'

Case Reports

P.B., the first child, was admitted to the London Hospital, E.1, on July 4, 1939, under Dr. A. G. Maitland-Jones for investigation.

The patient was born on May 14, 1939, at home by instrumental delivery. The birth weight was 4½ lb., and she was one month premature. She had difficulty in swallowing since birth. She took a long time over her feeds, and had choking attacks while taking them. On July 2, 1939, she went blue and collapsed while being fed.

On admission her temperature was 98° F., and respirations 52 per minute. Definite stridor was present. She was fairly well nourished. The throat was normal on ordinary examination. No enlarged glands could be felt. Marked recession of the ribs on both sides was a feature. The percussion note was dull with a few crepitations at the right base. The heart, abdomen, and nervous systems were normal.

The child had various attacks of stridor while in the ward, and was tube-fed owing to the difficulty in feeding. She was distressed on coughing. Laryngoscopy was carried out under an anaesthetic. Shortly after the examination, the child's condition deteriorated with the development of pyrexia and marked dyspnoea. On the day following laryngoscopy, July 21, 1939, she died.

The post-mortem examination showed a fissure in the mid-line of the uppermost part of the posterior wall of the larynx, running down to the level of the cricoid and true vocal cords. The arytenoids were completely separated by the fissure. The true and false cords were not abnormal. The epiglottis seemed abnormally long.

A.B., the second child, was admitted to Hillingdon Hospital, Uxbridge, on Dec. 24, 1940, aged four days.

This infant, also a girl, was born at full-term on

Dec. 21, 1940, at home. The history was that the child had been wheezy.

On admission it was found that there was no intercostal retraction when crying. The heart was normal. The chest was normal. The throat showed a highly arched palate with a very small entrance to the pharynx. Nothing abnormal was found in the abdomen or in the central nervous system. An extra toe was noted on the right foot. A radiograph of the chest on Dec. 30, 1940, showed normal aeration of both lungs.

Breast feeding was continued. When feeding or crying there was definite difficulty on inspiration, accompanied by crowing. The respirations were noiseless when the child was asleep. On Jan. 1, 1941, she was discharged home.

The child was readmitted to Hillingdon Hospital on March 13, 1941. All along she had gained weight slowly and during the two weeks before admission she had lost some weight and there had been a small amount of vomiting. On the evening of March 2, 1941, she had been coughing, and during the night she had had a choking fit, hence her readmission.

Examination on admission showed the general condition to be surprisingly good, and the child was taking feeds well. Laryngeal stridor was still noted, chiefly when crying. The chest was clinically clear.

On March 13, 1941, direct laryngoscopy was carried out by Mr. G. W. Duncan under general ether anaesthesia. A narrow glottis was seen with no evidence of polypi. The aperture was gently dilated. As a result of this dilatation, the cyanotic attacks ceased, although stridor was still present except when sleeping. The child however developed some degree of bronchitis, but the chest was clinically clear on discharge on April 6, 1941.

She subsequently attended the out-patient department, but was readmitted on May 20, 1941, at the age of five months for further investigation and dilatation. The weight on admission was 9 lb. 15 oz. Laryngoscopy was carried out by Mr. L. Fatti on May 26, 1941, under general ether anaesthesia, and the report was: ' Larynx apparently normal, though small. No polypi visible.' The larynx was dilated.

On the same evening as the examination the child died suddenly after a convulsion, the cause of which was not clear.

The post-mortem examination by Dr. J. S. B. Bray showed a cyanosed child. The brain was normal. There was no abnormality of the heart. The lungs were oedematous. The larynx was stenosed in its upper portion.

B.B., the third child, also a girl, was born in Hillingdon Hospital on Oct. 21, 1942, with a birth weight of 7 lb., the birth being normal. In view of the previous family history, a careful watch was kept on the child, and it was noted on the case sheet, when the mother and child were discharged from hospital, that there had been ' normal respirations since birth without stridor.' No stridor developed and this child remains perfectly fit.

D.B., the fourth child, a girl, was born at home on Sept. 24, 1947, her birth weight being 6 lb. She was entirely breast-fed from the beginning, and the birth weight was regained by the fourteenth day.

The infant was first seen at the out-patient department of Hillingdon Hospital on Oct. 27, 1947, aged five weeks, having been referred to me by Dr. Kate Glyn-Jones. The mother had noted that the child seemed unable to cry loudly and had been hoarse. Otherwise the mother was not unduly worried. During the third week the child gained 3 oz., and during the fourth week gained 5 oz. on the breast. There had been no vomiting.

A general physical examination showed a small, puny infant. The head circumference was $13\frac{1}{8}$ inches. The anterior fontanelle admitted three fingers. The cry was feeble. There was no clinical anaemia. No marked micrognathia was detected. Definite inspiratory laryngeal stridor was present without distress, but accompanied by slight indrawing of the chest wall. The heart sounds were normal and the chest clear. The abdomen was normal. The ears were dry. The throat was apparently clear.

A radiograph of the chest on Oct. 27, 1947, showed the lungs to be clear, but the bifurcation of the trachea was set at a more acute angle than normal. The child continued to attend the out-patient department regularly.

On Jan. 5, 1948, she was screened by Dr. S. A. Maddocks and a barium swallow was given. A right mid-zone pneumonic consolidation was present. The thymus was not enlarged radiologically. The trachea was of normal calibre, but there was apparently a marked laryngeal stenosis. There was no obstruction to the passage of barium down the oesophagus, but definite posterior notching of the oesophagus was noted. This suggested an aberrant vessel passing behind the oesophagus.

In view of the unhappy result of laryngoscopy in the two previously affected children, no attempt was made to examine this child by direct laryngoscopy. On Jan. 5, 1948, aged three months, she was admitted to Hillingdon Hospital. On examination she was found to be a very small child with a lusty cry. Continual mild stridor was present but the colour was good. The skull circumference was 14 inches. The anterior fontanelle admitted three fingers, and the skull bones were firm. The heart sounds were normal in all areas. The chest showed slight dullness on percussion over the right mid-zone posteriorly with occasional scattered rhonchi over both lungs. The throat showed relatively enlarged tonsils. The abdomen was poorly covered. There was no splenic enlargement. Neck rigidity was present, and the knee jerks both brisk.

The pneumonia was treated with both penicillin and sulphadiazine, and the child improved. Considerable head retraction remained constantly and typically present, the cerebrospinal fluid being normal. She was eager for her feeds, but tended to choke readily shortly after feeding had begun. Owing to repeated choking attacks feeding took a long time.

On Jan. 15, 1948, the Kahn test was negative.

A further radiograph (Jan. 14, 1948) showed marked clearing of the pneumonic consolidation.

The child's general condition remained more or less the same until Jan. 28, 1948, when she developed a temperature of 102° F., and became sunken and dyspnoeic. Another attack of pneumonia was suspected, and by Jan. 29, 1948, the percussion note was impaired over the left upper lobe anteriorly and there were many crepitations over the left lower lobe and in the left axilla. A few moist accompaniments were also present over the right base.

She went rapidly downhill and, in spite of treatment, died on Jan. 29, 1948.

NECROPSY : CRANIUM. The meninges were healthy, and there were no visible lesions in the brain. Mouth. The tongue was normal, as also was the pharynx. The thyroid was normal.

CHEST. The thymus was normal, and no adhesions or fluid exudates were present.

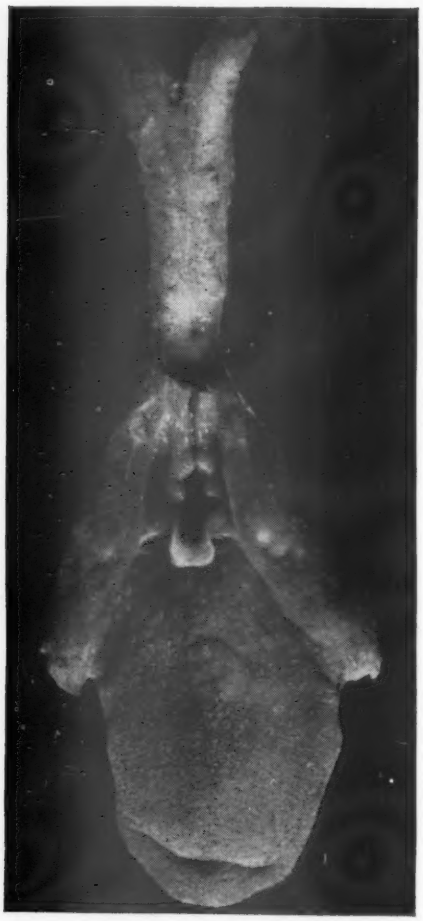

FIG. 1.—Larynx and trachea from the fourth child. The laryngeal aperture has been widened by fixative action.

FIG. 2.—Aorta (posterior view) from the fourth child, showing the abnormal origin of the right subclavian artery.

LARYNX. The larynx as a whole was unduly narrow. The upper aperture was small, but there was no web or fissure present (fig. 1).

TRACHEA. The mucous membrane was normal. The bifurcation was an acute V-shape, and the primary bronchi somewhat lengthened. Both lungs contained areas of bronchopneumonia, and adjacent lung tissue was rather emphysematous in appearance. No caseous glands were seen and no evidence of tuberculosis found in the lungs.

CARDIOVASCULAR system. The pericardium was normal. The heart appeared to be normal and without congenital defects. The innominate artery did not divide and carried on upwards as the right carotid artery. The left carotid and left subclavian arteries were normal. From the descending thoracic aorta, a vessel arose at about the level of the second or third thoracic vertebra, and crossed the midline behind the oesophagus to run slightly upwards as the right subclavian artery (fig. 2). Below this level the aorta was quite normal.

ABDOMEN. The liver was slightly enlarged and toxic in appearance. The gall bladder and extrahepatic ducts were normal. The pancreas, adrenals, both kidneys, urinary tract, uterus, were all normal. The oesophagus was normal, as also the stomach, which contained a recent feed. In the intestine there was a short, broad Meckel's diverticulum.

Histological investigation showed in the lung a widespread bronchopneumonia with bronchioles full of polymorphic exudate; a congested liver with some toxic changes in hepatic cells, but biliary ducts healthy; in the kidney normal glomeruli with

moderate degenerative changes in the epithelium of tubules. The pancreas was normal histologically.

The diagnosis was bilateral bronchopneumonia, with the associated defects of congenital narrowing of the laryngeal aperture, abnormal origin of the right subclavian artery of dysphagia lusoria type, and Meckel's diverticulum.

It was difficult to decide to what extent the abnormal origin of the right subclavian artery in the last child could account for the symptoms. This type of vascular anomaly can produce oesophageal pressure with resultant dysphagia but does not commonly, at any rate, produce stridor. There is no pulling forward of the trachea as is present when the trachea is completely encircled by a vascular ring, as in the double aortic arch anomaly. In the last case in this family the condition of the larynx was sufficient to account for the stridor.

It should be mentioned that an abnormal origin of the right subclavian artery may readily be missed, as indeed may any anomaly of the great vessels. During life a barium swallow is the means of detecting it and at necropsy its discovery entirely depends upon the technique employed in removing the thoracic contents.

Gross (1946) has reported what he believes to be the first case of dysphagia lusoria treated surgically This was an infant aged four months who presented with a history of difficulty in feeding. Examination of the oesophagus after swallowing barium showed indentation of the posterior oesophageal wall at the level of the third thoracic vertebra. Double ligation of an anomalous right subclavian artery near its aortic source was carried out, and after division between the ligatures the distal portion of the divided vessel was permitted to retract to the patient's right and beyond the oesophagus. There was no further difficulty experienced with feeding after the operation. It should be noted, however, that there was no mention by Gross of stridor having occurred at any time in his case.

In a Moynihan Lecture, delivered in 1947, Blalock and Bahnson reporting a series of six hundred and ten cyanotic congenital heart cases operated upon, stated that in twenty-six of these there was a retro-oesophageal subclavian artery. They mentioned that for some unknown reason these retro-oesophageal arteries were unduly thin-walled. In one patient in whom a retro-oesophageal subclavian artery was anastomosed to the pulmonary artery, there were suggestive signs of tracheal obstruction post-operatively owing to the vascular ring created by the anastomosis.

Summary

Reference has been made to the more important papers illustrating the development of our knowledge of laryngeal stridor in early infancy.

The clinical notes and post-mortem findings of three children in one family, all showing congenital stridor, are presented.

The last case was shown to have an abnormal origin and course of the right subclavian artery. Two of the children died shortly after laryngoscopy.

I have to thank Dr. W. Arklay Steel, medical director of Hillingdon Hospital, for permission to publish this paper; I am much indebted to Dr. C. G. Barnes for his advice; and to Dr. A. G. Maitland-Jones for permission to quote from his notes regarding the first case.

I am grateful to both Dr. H. Rogers, who carried out the post-mortem examination in the last case, and Dr. W. R. May for their help and interest. The photographs are the work of Mr. E. A. R. Banks.

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POLYARTERITIS IN CHILDHOOD

BY

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With increased study of the mesenchymal tissues and their special reactions to toxic, infective, and allergic factors, the particular pathological grouping, in regard to the place in which the blood vessels are directly involved, has been widely considered. A considerable literature dealing with the pathology and the clinical manifestations of polyarteritis has shown clearly that the connective tissue elements in the vessel walls are, under certain conditions, highly susceptible to inflammatory and necrotizing agents. It must be admitted that the morbid anatomy has been clearly defined, and that certain clinical and experimental observations have lead to some support for an etiological basis of allergy. Nevertheless the precise relationships cannot be considered to be fully understood. In fact it is quite evident that in this field of pathology there is still ample scope for classification, and particularly so in as much as a similar tissue response mechanism is concerned in a wide variety of clinical forms of disease. Polyarteritis may in some cases exist as the only apparent tissue manifestation, but in others there is a more widespread mesenchymal tissue reaction, and an infinity of graduations may occur.

Teilum (1946), in discussing lupus erythematosus disseminatus and related diseases, notes the peculiar fibrinoid necrotizing processes in free connective tissue and in the walls of blood vessels together with miliary epithelioid cell granulomata in the serosa; he proceeds to consider ' a state of allergy induced by specific processes of immunity ' as a basis for the tissue changes. In contrast to lupus erythematosus disseminatus Teilum considers rheumatic fever to be etiologically and clinically a type of specific lesion. However, this author is mindful of the close pathological relationship of lupus erythematosus disseminatus, polyarteritis and arteriolotis granulomatosa (allergica), and inclines to the view that there is a group of ' para-rheumatic ' diseases of similar pathogenesis and different etiology, but possessing in common a state of hypersensitivity to bacterial toxins and allergens.

The clinical and experimental observation of Rich (1942) has elucidated possible etiological factors involved in polyarteritis nodosa. There is in these experiments ample evidence for Rich's confident belief that arterial lesions of this type are manifestations of anaphylactic hypersensitivity. Undoubtedly there are widely different types of sensitizing antigens which have the potentiality of causing polyarteritis in man. Galán (1945), after experimental evidence, is of the same opinion. There is, however, the necessary adjuvant factor of constitutional and special tissue susceptibility which tends to defy clinical recognition.

Linkages in pathology are revealed in the cases of rheumatic carditis associated with characteristic polyarteritis nodosa (Neale and Whitfield, 1934). Friedberg and Gross (1934) also describe four cases of periarteritis nodosa in rheumatic fever in which Aschoff bodies were demonstrable in the myocardium. Buckley (1946) points out that in the Libman-Sacks syndrome vascular changes identical with those seen in polyarteritis nodosa are sometimes present, and he records an example in which generalized vasculitis, in association with ulcerous dermal changes, were present; he considered the whole pathology to be a sequel to chronic focal infection.

The experimental work of Selye (1946) is remarkable in so far as it reveals, in certain animals, an arterial reaction with nodular inflammatory changes following injections of adrenal cortical steroid hormone or anterior pituitary extract; this effect is intensified if the animal is receiving excessive amounts of salt. Selye advances the view that in some susceptible persons an overdosage of endogenous cortical hormone, such as may occur in reaction to a sore throat, a nervous shock, or an exposure to cold, etc., may determine the occurrence of tissue responses indistinguishable from that of rheumatic fever and periarteritis nodosa.

It is significant that eosinophilia is only exceptionally present in childhood cases of polyarteritis nodosa, and this bears no inherent relationship to the degree, extent, distribution, or the severity of the lesions. In Wilmer's (1945) two very severe infant cases there was no increase in eosinophils. In a series of twenty-eight cases of polyarteritis in children, two only also had asthma, whereas of three hundred at all ages with the same arterial disease, fifty-four had asthma and 94 per cent. of these revealed hyper-eosinophilia (Wilson, 1945). In the absence of associated asthma, polyarteritis is significantly dissociated from eosinophilic response.

Although the researches of Rich and others have placed a definite allergic responsibility in polyarteritis, clinical observations are by no means so clear, possibly owing to intrinsic difficulties in

assessing prodromal phenomena in the disease or to the virtual impossibility of exploring sufficiently, at a clinical level, allergic mechanisms of this order. It is of some interest that polyarteritis in childhood is rarely associated with any known common form or type of allergy. This suggests that in polyarteritis a specially individualized arterial receptor mechanism exists for allergen action. By and large, the incidence of this unusual vascular susceptibility, at any age group, appears to be considerably less than the clinical allergies of other tissue systems.

From the clinical aspect no age group appears to be immune in regard to arterial susceptibility and the condition is probably not of great rarity in infancy. The bizarre nature of the clinical manifestations may well be confusing, but Wilmer (1945) has described two cases of polyarteritis in the first month of life. In each of these two infants sepsis was present and the nature of the violent and fulminating course of the disease would indicate a probable peculiarly inherent arterial tissue sensitivity. The intensity of this susceptibility is revealed in the case of a baby aged nine months who died suddenly two months after an attack of acute tonsillitis: the coronary arteries were severely affected with nodular arteritis (Diaz-Rivera and Miller, 1946).

Extended search will probably reveal that polyarteritis is more frequently present than is usually considered. Moreover, there is a strong tendency to some special sectional distribution of the arterial inflammatory reaction in different patients or the effects are dominantly represented in a particular visceral, neural, or cutaneous zone. The prognosis frequently depends upon the more particularly individualized locality of the disease and, in fact, clinical studies suggest that focal arterial reactions, e.g. cerebral, renal, coronary, may be more devastating than quite extensive cutaneous involvement. This tendency to a local dominance is well illustrated by Malamud (1945), who describes a child aged five years in whom polyarteritis selectively involved the meningeal vessels with resultant cerebral damage and decerebrate rigidity. Ophthalmoscopy may be specially helpful; inspection of the choroidal arteries may show fusiform aneurismal dilatations (Goldsmith, 1946) or degrees of retinal detachment (Sampson, 1945).

Although visceral involvement is rightly regarded as a constant menace in polyarteritis, and Bradley (1947) considers the outstanding and special danger to the renal vascular mechanism, cutaneous lesions may exist as the only apparent pathological distribution. Downing (1947) believes that the cutaneous arteries are associately affected in 40 per cent. of all cases, but it has no special dominance in any age group.

On clinical and pathological evidence the disease may have an exclusively subcutaneous localization. Miescher (1946) described four examples of this kind, and in one form the leucocytoclastic vasculitis of the subpapillary vessels is likened to the papulohaemorrhagic exanthema of the type peliosis rheumatica. In another, the appearances were similar to that of a papulonecrotic tuberculide, and yet in the others there were variable histological appearances, sometimes approaching granulomatous changes.

The cutaneous type of polyarteritis nodosa may reveal severely acute and alarming effects, more especially owing to the possibility of ischaemic necrosis. Veran (1945) observed massive gangrene of the foot as a result of the disease in a baby aged fifteen months, but in whom general recovery occurred after several months' illness. Particularly mutilating effects were observed by Galán in a boy who developed gross necrosis of the abdominal wall and gangrene of the terminal phalanges of the fingers. In this case there was also a 'livedo reticularis' and a phasic variation of 0-10 per cent. in the eosinophil polynuclear leucocytes. Despite the severe cutaneous effects, slow but satisfactory recovery occurred. Peripheral panarteritis following scarlet fever is recorded by Hoyne and Smoller (1941).

An appraisal of the clinical signs of the disease in childhood (44 cases) revealed purpuric rash in 34 per cent., other rashes, including urticarial type, in 27 per cent., and palpable nodules in 4·5 per cent. (Keith and Baggenstoss, 1941).

The cutaneous form of polyarteritis offers special advantages in the clinical study of the disease.

Case Reports

Case 1. D.J.W. was a girl aged nine years, the first child of two. There was no family history of disease. The child's past history was one of pertussis and measles only. In May, 1943, the present illness began. The child developed a fairly severe acute streptococcal tonsillitis with moderate submaxillary adenitis. A few days later 'rheumatic' pains commenced in the shoulders, back and legs, and shortly afterwards an 'unusual' skin rash made its appearance. The child felt generally ill and remained in bed until admitted to hospital. Under hospital observation it was clear that a somewhat unusual syndrome was present. She was irritable and in continued discomfort and had variable limb pains. The two outstanding visible signs were the persistent flexural position of the limbs in bed and a very marked mottled rash all over the body, especially marked on the limbs. The rash was similar to that of 'cadaveric staining', and was striking in so far as the face was also affected and the intensity varied from day to day, sometimes being peculiarly prominent and unlike any other known rash. There was a fluctuating appearance and disappearance of subcutaneous tender nodules which left no doubt that the subcutaneous arteries were affected by acute focal, nodular, and inflammatory changes. There was never, in this girl, any evidence of tissue or skin necrosis, which presumably indicated that the arterial lumen was in no area

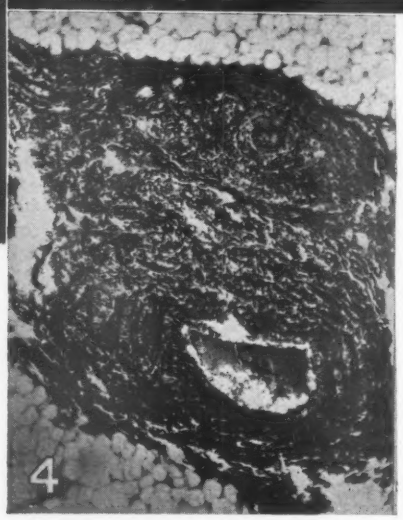

FIG. 1.—D.J.W. A few weeks after the onset of acute polyarteritis. Note the flexion attitude and the mottled rash on the limbs.

FIG. 2.—D.J.W. in a phase of clinical improvement. Rash and nodules visible.

FIG. 3.—D.J.W. Two years later. No signs of disease, but 'meshwork' staining of lower limbs still present.

FIG. 4.—D.J.W. BIOPSY OF SKIN.—Proliferation of subendothelioid connective tissue of the intima; oedema and necrobiotic changes in the media with disarrangement of the muscle fibres, cellular infiltration, and fibrosis of the adventitia. Occasional necrosis of perivascular tissue with invasion of granulation tissue with foreign body giant cells. Elastica was intact in some arteries and disrupted in others.

FIG. 5.—H.J. The early acute phase. Note flexion posture; cutaneous nodules, and characteristic rash on the limbs and face.

FIG. 6.—H.J. A phase of great clinical improvement. Note residual appearance of limbs and slight oedema of the feet.

FIG. 7.—H.J. Dermal necrosis in final acute phase. Note nearby arterial nodules.

FIG. 8.—H.J. Ischaemic effects of fingers in final acute phase of necrotizing obliterative arteritis.

obliterated. There was no evidence at any time of any arterial disease in the deeper structures or in the viscera. Repeated examination revealed no evidence of renal involvement and the heart remained clinically and electrocardiographically normal. The outstanding clinical feature was the persistent rash, traces of which can still be seen (three years later). Considerable general wasting accompanied the illness, and over an observed course of eight months (May, 1943, to February, 1944) there was an undulating pyrexia with maximal levels around 103°. The pulse rarely reached above 120 and the respiratory rate was 30. There was no abnormal sweating. There was a persistent leucocytosis of 15,000 per c.mm., but eosinophils were never more than 4 per cent. Blood cultures were sterile.

A biopsy of the skin (forearm) was done on March 14, 1944. The majority of the arteries in the subcutaneous tissue, and in a lesser degree those of the cutis vera, showed severe pathological changes. There was proliferation of the sub-endothelial connective tissues of the intima, necrobiotic changes of the media, and proliferation of the vascular granulation tissues of the media with much disarrangement of the muscle fibres. The cellular infiltrations consisted of neutrophil polymorphs, lymphocytes, monocytes, and a few eosinophils. The infiltration extended sometimes throughout the whole vessel wall and often diffusely into the perivascular connective tissue. Foci of extensive necrosis were seen in the perivascular tissue, and a form of giant cell granulation tissue could be seen in some areas. There was occasional disruption of the muscle fibres. The picture was that of panarteritis nodosa.

From time to time the child had severe limb pains and very strongly resented being handled or moved. Skin nodules appeared and disappeared, and the whole illness presented considerable phasic variability. Many symptomatic remedies were prescribed, but it seemed clear that the disease was refractory. In view of the possibility of retained tonsil sepsis, tonsillectomy was performed, but no appreciable improvement occurred. Three months later a very severe exacerbation of all the symptoms and signs appeared with some oedema of the feet. The mesh-like general rash and erythematous nodular foci again became prominent. The clinical progress indicated a waxing and waning of arteritis nodosa of cutaneous form.

After a prolonged stay in hospital, gradual improvement occurred, although limb pains occurred when she was unduly warm in bed. The rash gradually diminished.

In the following two years occasional crops of periarterial nodules made their appearance and were usually accompanied by limb pains and some days of immobility. Finally, in 1945, she seemed to be free from all effects of the prolonged illness. One year later she developed diphtheria and was given adequate doses of anti-serum without any adverse effects. In 1948, at the age of thirteen years, she was clinically well. Puberty occurred normally and menstruation appeared.

Case 2. H.J. was a boy aged eight years and the fifth child of seven. There was no family history of disease, and the child had a past history of measles only.

This boy was admitted to hospital in June, 1943, seventeen days after a sore throat, and actually during the same time as the previous case. The clinical picture at that time was identical. Thirteen days before admission he had received sulphonamide and three days later a macular rash appeared all over the body and also numerous red-purple focal swellings. Pains in the joints, varying in the manner of rheumatic fever, also occurred. There was no evidence of any visceral disturbance.

Histology of a subcutaneous nodule confirmed the diagnosis of periarteritis nodosa. The blood showed a fluctuating neutrophil leucocytosis, reaching a maximum of 21,400, but at no time did the eosinophils exceed 1·5 per cent.

This boy was particularly troubled with limb pains, and on several occasions temporary joint swellings with small effusions appeared. Clinically the intensity of the disease was more severe in this case. The ' mesh-work ' erythema was very marked and quite prominent on the face. The feet were swollen and very painful and there were many subcutaneous nodules along the course of the arteries. The heart was clinically normal and electrocardiograms were normal. A variable pyrexia with maxima of 103° continued over many weeks. Intensive doses of penicillin had no favourable effect, and sulphathiazole was given without any response. Over a period of one year the disease varied in intensity, but eventually he became ambulatory and comfortable, and his mother thought he was very well. However, a few cutaneous arterial nodules continued to appear at intervals and the ' cadaveric ' staining on the limbs was persistent. Eighteen months after the onset the boy was gaining weight and had no symptoms, but he had clearly not reached a phase of real health. Three weeks later he had a ' cold ' and a recurrence of the previous limb pains and a marked accentuation of the cutaneous erythema. His condition quickly deteriorated and necrosis appeared in the fingers and in some other skin areas. Necropsy revealed no evidence of any visceral involvement in the arterial disease. There was no tonsil sepsis or any other evidence of active focal infection. There was no renal pathology.

Discussion

These two cases of polyarteritis indicate (1) that the disease reaction may be apparently confined to a particular section of the arterial system; (2) that such pathological response may have a prolonged and clinically fluctuant course and be compatible with a satisfactory recovery without sequelae; or,

(3) by an acute exacerbation, lead to quickly spreading ischaemic necrotic changes.

The clinical features of the dermal form of arteritis are distinguishable more particularly by the occurrence of painful nodular swellings visible and palpable in the skin. The arterial nodules may be extremely numerous and yet apparently the incidence of intra-arterial thrombosis is minimal. This is particularly indicated in the case of D.J.W., in whom it was not possible at any time during her relapsing illness of many months to detect any effects arising out of lumenal occlusion. The type of generalized rash is peculiarly characteristic in its meshwork of bluish discoloration and resemblance to that seen in cadaveric staining; this is most marked on the lower limbs and is very persistent throughout, and for some time after the active phase of the disease has subsided. In the two cases here recorded the face showed a variable general swelling in relationship to the periodic intensification of the rash. The mucous membranes were unaffected but conjunctival suffusion was present.

No definite etiological factors were discovered, but in each case the arteritis was preceded by rather severe sore throat, so that bacterial toxaemia was probably causally related. In neither case could any definable allergic susceptibility be established in an individual or familial basis. The bouts of fever may be merely related to pyrogenic products in the necrotizing arteritis.

Treatment

The life history of the disease and its refractory nature to any known specific therapeutic measure reduces the treatment to symptomatic remedies for pain, insomnia, etc. The tendency for lower limb contractures, owing to prolonged decubitus immobilization, must be overcome by suitable temporary splinting. The peripheral vascular ischaemic effects might be in part remedied by nicotinic acid. Benadryl and other anti-histamine drugs have also received clinical trial, without, however, any detectable effect.

Summary

Some considerations of the possible etiological relationships in polyarteritis in childhood are presented and two cases of the ' dermal ' form are recorded. A prolonged illness, with an ever-present menace of possible visceral involvement, was successfully negotiated and clinical recovery without sequelae occurred in one child. In another child the prolonged and variable clinical course seemed to have reached a favourable outcome, but unexpectedly a sudden and intense relapse quickly progressed to acute obliterative cutaneous arteritis and spreading ischaemic necrosis.

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BRITISH PAEDIATRIC ASSOCIATION

PROCEEDINGS OF THE TWENTIETH GENERAL MEETING

The twentieth annual meeting of the British Paediatric Association was held at Windermere on May 4, 5 and 6, 1949.

Business proceedings: The President, Dr. H. T. Ashby, was in the chair, and the following members were present:

Drs. F. M. B. Allen, E. C. Allibone, H. T. Ashby, C. Asher, H. S. Baar, J. M. Bligh, F. Braid, J. V. Braithwaite, R. W. Brookfield, D. Browne, H. C. Cameron, W. H. P. Cant, N. B. Capon, I. A. B. Cathie, C. Chisholm, W. R. F. Collis, T. Colver, B. D. Corner, J. Craig, W. S. Craig, J. Crooks, V. M. Crosse, G. Davison, R. H. Dobbs, E. Dott, A. C. Doyne Bell, R. W. B. Ellis, P. R. Evans, G. B. Fleming, F. J. Ford, A. W. Franklin, D. Gairdner, W. F. Gaisford, S. Graham, C. K. J. Hamilton, A. C. Hampson, E. W. Hart, J. D. Hay, J. L. Henderson, D. V. Hubble, J. H. Hutchison, R. S. Illingworth, N. M. Jacoby, R. C. Jewesbury, H. E. Jones, A. Lichtenstein, R. C. Lightwood, A. MacGregor, H. M. M. Mackay, A. G. Maitland-Jones, F. J. W. Miller, A. Moncrieff, A. E. Naish, A. V. Neale, G. H. Newns, D. N. Nicholson, J. N. O'Reilly, C. G. Parsons, L. Parsons, W. W. Payne, C. P. Pinckney, C. T. Potter, B. Schlesinger, W. P. H. Sheldon, U. Shelley, W. C. Smallwood, J. M. Smellie, J. F. Smith, R. E. Smith, R. E. Steen, K. H. Tallerman, M. L. Thomson, C. W. Vining, H. K. Waller, J. F. Ward, A. G. Watkins, K. D. Wilkinson, T. P. Williams, M. J. Wilmers, W. G. Wyllie.

The Association had the honour of entertaining thirty Swedish paediatricians and twenty other guests.

The minutes of the last annual general meeting were approved.

ELECTION OF OFFICERS: The following were unanimously elected by ballot for the year 1949-50:

PRESIDENT: Dr. A. G. Maitland-Jones.
TREASURER: Dr. R. C. Lightwood.
SECRETARY: Prof. Alan Moncrieff.

EXECUTIVE COMMITTEE (to replace those retiring):
REPRESENTATIVE FOR PROVINCES: Prof. R. S. Illingworth.
REPRESENTATIVE FOR IRELAND: Prof. F. M. B. Allen.

CO-OPTED SINCE THE LAST ANNUAL GENERAL MEETING:
REPRESENTATIVE FOR LONDON: Dr. R. E. Bonham Carter.
REPRESENTATIVE FOR PROVINCES: Dr. D. V. Hubble.

ELECTION OF NEW MEMBERS: The following were elected by ballot to membership of the Association:

(a) HONORARY MEMBERS:
Dr. H. T. Ashby.
Sir Allen Daley.
Dr. A. C. Hampson.
Dr. K. D. Wilkinson.

(b) CORRESPONDING MEMBERS:
Dr. S. L. Ludbrook (Auckland).
Prof. A. Ylppö (Helsinki).

(c) ORDINARY MEMBERS:
Dr. I. M. Anderson (London).
Dr. D. Court (Newcastle-on-Tyne).
Dr. E. Mildred Creak (London).
Dr. F. F. Kane (Belfast).
Dr. P. MacArthur (Glasgow).

THE TREASURER'S REPORT was received and approved.

THE REPORT OF THE EXECUTIVE COMMITTEE for the year was received and approved and is printed below.

NEXT PLACE OF MEETING: It was reported that it was still hoped to have a joint meeting with colleagues from Canada and the time and place of meeting depended upon this.

Report by the Executive Committee 1948-49

Since the last annual general meeting held at Windermere in April, 1948, the Executive Committee has met on four occasions. The following is a brief summary of the main activities during the year.

1. APPOINTMENTS AND DISTINCTIONS: Congratulations were sent to Professor J. C. Spence on his receiving the honorary D.Sc., Western Australia, and to Dr. F. M. B. Allen on his election to the new chair of child health in Belfast. The Executive Committee also noted with pleasure the promotion of Sir Wilson Jameson to G.C.B. and the knighthood conferred on Sir William Gilliatt, P.R.C.O.G. The following public appointments of members of the Association were also noted with satisfaction:

Professor J. C. Spence to the Central Health Services Council and to the Advisory Committee on Maternity and Midwifery.

Dr. W. Sheldon as paediatric adviser to the Ministry of Health and as a member of the Tuberculosis Advisory Committee.

Dr. A. G. Watkins to the Dental Advisory Committee.

Prof. A. Moncrieff as Chairman of the Home Office Central Advisory Council on Child Care.

The Association will also wish to congratulate Prof. J. C. Spence and Prof. A. Moncrieff on each

being awarded a Dawson Williams Prize of the British Medical Association.

The Association also congratulated Dr. Catherine Chisholm, an honorary member, on election to the F.R.C.P. for special distinction.

2. OBITUARY: The Association lost during the year Reginald Miller, an honorary member, one of the original members of the Association and for many years joint editor of the 'Archives of Disease in Childhood.' The death of Dr. F. Tisdall, a corresponding member of Toronto, occurring on April 23, 1949, was also noted with sorrow.

3. RESIGNATIONS: Dr. H. L. Wallace resigned on going to South Africa, and Dr. Ian Gordon on giving up his work with children.

4. NEW SOCIETIES: The Executive Committee has watched with interest the development of several flourishing regional paediatric societies in accordance with the policy approved last year. Greetings have been sent to newcomers, including the South African Paediatric Society, the Portuguese Paediatric Society, and the Scottish Surgical Paediatric Club.

5. GIFT TO THE ASSOCIATION: Members will note the new gavel for the use of the chairman, presented by Dr. Henry Helmholz.

6. VISIT TO SWEDEN: Twenty-five members of the Association visited Sweden in the summer of 1948 and greatly enjoyed the charming and generous welcome they received. It is with very great pleasure that the Association is able to welcome a party of Swedish colleagues to the annual meeting.

7. MEMBERSHIP: Nominations this year again far outnumbered the places available and the Executive Committee has set up a special sub-committee to discuss the whole policy of membership.

8. ARCHIVES OF DISEASE IN CHILDHOOD. The Association will learn with regret of the resignation of Professor R. W. B. Ellis to take effect at the end of 1949. Dr. P. R. Evans and Dr. I. A. B. Cathie have been proposed as joint editors, and for the Editorial Committee the names of Professors R. W. B. Ellis and W. F. Gaisford to take the place of Sir Leonard Parsons and Dr. C. F. Harris have been put forward to the British Medical Association.

9. STANDING COMMITTEES AND REPRESENTATIVES ON OTHER BODIES: In close collaboration with the Association of Sick Children's Hospital Nurses the nursing sub-committee has continued to urge the importance of the continuation of some form of special training for the nurse in the care of the sick child. The Hospital Architecture and Cross Infection Committee has been discontinued, and a final report on cross infection is being prepared for publication. A new committee to conduct a survey of growth in children has been formed to combine with representatives of the Ministry of Health and the Ministry of Education, and for this investigation an expenses grant has been most generously made to the Association by Messrs. A. and R. Scott, Ltd. The child psychology sub-committee has collaborated with the National Council for Mental Health in regard to a policy for the future organization for child guidance. The Public Health Committee of the British Medical Association has again co-opted a member of the Association. Professor W. S. Craig was appointed to represent the Association at the Royal Sanitary Institute Congress at Brighton and Dr. R. H. Dobbs to be a 'standing' delegate for meetings arranged by the National Association for Maternity and Child Welfare.

10. WINTER MEETING, 1949. Arrangements are being made for a joint meeting with the Maternity and Child Welfare Group, the School Medical Officers' Group, and the Fever Hospital Medical Officer Group of the Society of Medical Officers of Health to be held at B.M.A. House on Friday and Saturday, Nov. 25 and 26, 1949. The programme will include a discussion on the organization of child health services, the Still Lecture by Professor St. G. Huggett, a session for short communications, and a clinical demonstration.

11. INTERNATIONAL CONGRESS, 1950. The date of the Sixth International Pediatric Congress in Zurich has been changed to July 24 to 28, 1950. The Executive Committee has supplied, at the request of Professor Fanconi and his associates, the names of suitable participants in the proposed programme.

12. ANNUAL MEETING, 1950. The suggestion for a joint meeting with Canadian colleagues immediately before the Zurich meeting is still being actively pursued. The date would be approximately July 19 to 21, 1950. A suitable place has not yet been arranged.

13. NEONATAL JOINT COMMITTEE REPORT. The Joint Report of the Royal College of Obstetricians and Gynaecologists and the Association on 'Neonatal Mortality and Morbidity' was published by the Ministry of Health in March and has received favourable comment in the press.

14. EXPENSES OF COMMITTEE MEMBERS. It has been decided that expenses over and above the sum of £20 per annum incurred by members of the Executive Committee through attending meetings of the committee, other than the meeting held at the same place as the Annual General Meeting, will be repaid to them by the Hon. Treasurer out of the funds of the Association. This decision also applies to members of the Standing Committees appointed by the Executive Committee and to representatives of the Executive Committee attending other bodies.

ALAN MONCRIEFF.

Communications

1. DR. E. MANNHEIMER (Stockholm): Cardiac Catheterization in Congenital Heart Disease.' To be published in the December issue.

2. DR. W. SHELDON (London): 'Coeliac Disease: a Relation between Dietary Starch and Fat Absorption.' See page 81.

3. DR. T. COLVER (Sheffield): 'Aspects of the Natural History of Pink Disease: One Hundred Personally Studied Cases.' This study comprised

fifty-six males and forty four females. Of these ninety-one were in the first, eight in the second, and one in the third year of life. Age incidence was maximal between four and ten months. There were four deaths. No particular seasonal incidence was noted. The average duration was 17·8 weeks, and was modified by hospital selection. For instance, cases referred to hospital early had an average total duration shorter than that of cases referred late, chiefly because cases referred late had already proved themselves refractory. As regards duration, therefore, cases referred early were considered more representative of the average. Average duration of cases seen within the first four weeks of the disease was 13·7 weeks, as opposed to twenty-two weeks for cases seen later.

The total duration of disease was not a satisfactory single measurement by which to compare managements, as there was no sharp end point. Duration from onset to the beginning of the recovery phase was, however, a better defined period, and plottings showed that the improvement began half-way through the disease. Once it occurs the mother can be reassured that, barring intercurrent infection, relapse is unlikely. The first stage of the disease was on the average shorter in the older cases.

A controlled series received weekly injections of vitamins B1 and B6 without demonstrable benefit.

4. DR. K. B. ROGERS (Birmingham, introduced by Dr. W. C. Smallwood): 'An Epidemic of Enteritis in Infants: a Bacteriological Study.' Bray, Giles, and Taylor had all found the same serologically specific type of coli associated with epidemics of gastro-enteritis. The same organism was found in three Birmingham hospitals, two of these having epidemics of gastro-enteritis. While its pathogenicity was not proved, because of its very intimate association with cases of gastro-enteritis and its absence in controls, this organism was followed to demonstrate the possible modes of spreading infection. In two hospitals its presence in dust and furnishings explained the possible spread within a ward or cubicle. Finding it on the communal broom and polisher, on a nurse's hand and shoe and on towels, showed ways of spreading infection throughout a cubicle ward.

The efficiency of a suction type cleaner was described: it retained infected dust without allowing any organism to escape; with it wards and cubicles could be cleaned without risk of spreading infected dust.

5. DR. J. P. M. TIZARD (London, introduced by DR. W. G. WYLLIE): 'Oesophageal Disorders in Childhood.' An account was given of some findings from a survey of fifty-four cases. Difficulties encountered in diagnosis were discussed.

The series included twenty-seven cases of stenosis, in ten of which the narrowing appeared to be at the site of the cardia in a short oesophagus. In the remaining seventeen it was not found possible to determine whether the stenosis was associated with a short oesophagus or whether it occurred in an oesophagus of normal length.

In contrast there was a group of twelve cases in which reflux of gastric contents led, in early life, to oesophagitis and haematemesis. On endoscopy the oesophagus was seen to be widely dilated at the junction of the oesophageal and gastric mucosae, and under fluoroscopy the distinctive reflux of the barium mixture from the stomach could be observed. The normal mechanism preventing such a reflux was discussed; it was significant that at least six of these cases were examples of short oesophagus with the cardia above the diaphragm.

Amongst the symptoms emphasis was laid on the frequency of projectile vomiting in infancy, both in the stenotic group and in the cases of incompetent cardia, as this had frequently distracted attention from the oesophagus.

The prognosis seemed rather better in the cases of incompetent cardia, in which haematemesis usually ceased when the child began to sit up, while vomiting lasted somewhat longer. In the majority of the stenotic group vomiting continued throughout childhood, but that recovery might ultimately take place without operative treatment was shown in three cases followed up into adult life.

6. MR. D. BROWNE (London): 'Two Cases of Stenosis of the Oesophagus.'

7. DR. J. H. HUTCHISON (Glasgow): 'Obstructive Emphysema in Primary Tuberculosis.' Obstructive emphysema arises when the air-spaces distal to an incomplete bronchial obstruction become ballooned by air which enters them during inspiration but cannot find egress during expiration, because in this phase the normal constriction of the bronchi causes the obstruction to become complete. This type of emphysema is more often due to primary tuberculosis than to any other cause in infancy and childhood in Great Britain.

Twelve such cases had been met with in the course of three years. Two cases were described in detail, including the radiological and bronchoscopic appearances. In both cases caseous tissue containing tubercle bacilli was removed through the bronchoscope.

The outstanding clinical features in all such cases were the asthmatoid wheeze, which is clearly audible at the open mouth, combined with hyper-resonance to percussion and diminished breath sounds on auscultation. The radiological features were increased translucency, and in severe cases, mediastinal shift to the opposite side, depression of the diaphragm, and widening of the intercostal spaces; all these signs are more marked during expiration.

8. PROFESSOR A. LICHTENSTEIN (Stockholm): 'The Treatment of Diabetes in Childhood.' To be published in the December issue.

9. DR. G. VAN SYDOW (Sundsvall): 'Rickets in the Newborn.' In a series of premature infants the serum values of phosphatase became much higher, and those of inorganic phosphorus and calcium much lower than normal during the first few months of life in infants fed exclusively on human milk. Large doses of vitamin D raised the calcium level

but did not affect the phosphatase and phosphorus levels, whereas cow's milk (i.e. supplementation with minerals) brought the phosphatase and phosphorus levels nearer to normal while leaving the calcium level unaffected. Supplementation with both vitamin D and cow's milk caused the values of all three substances to approach normal.

In a histological investigation of a series of newborn infants dying in the maternity hospital unmistakable signs of rickets were found in 57 per cent. of all cases. The incidence increased sharply with age.

In view of these findings it must be recognized that in many cases rickets is due to influences affecting the foetus before birth. Taking this into consideration a theory of the pathogenesis of early rickets is formulated and preventive measures are proposed, beginning during pregnancy and including both mineral and vitamin D administration.

10. DR. I. A. B. CATHIE (London): 'Bacterial Fibrinolysin.' To facilitate the passage of streptomycin into the gelatinous exudate at the base of the brain in cases of tuberculous meningitis the possibilities of bacterial fibrinolysin have been investigated.

Haemolytic streptococci produce a substance known as streptokinase, capable of causing lysis of fibrin clots formed from plasma. Pieces of fibrinous exudate from fatal cases of meningitis may also be lysed. Streptokinase appears not to be a true lysin but an activator of a naturally occurring profibrinolysin. It may be prepared by absorption from broth cultures of haemolytic streptococci with aluminium hydroxide and elution in phosphate buffer, and the substance is relatively non-toxic to animals. For standardization a fibrin clot is prepared from plasma roughly comparable to a cerebrospinal fluid spider's web clot. The concentration necessary for the lysis of such a plasma clot in one hour is determined, and for therapeutic trial one hundred times this concentration in 1 ml. was chosen, on the assumption that one hundredfold dilution with cerebrospinal fluid occurs on intrathecal injection.

Given therapeutically with streptomycin the streptokinase causes a pleiocytosis and increase of protein in the cerebrospinal fluid, thought to be due in part to the irritant action of the substance and in part to the release of cells and protein from the gelatinous exudate. Tubercle bacilli are also more easily seen and grown.

In a small series of cases treated by the combination of streptomycin and streptokinase the immediate results were considerably better than in a similar series treated with streptomycin alone. Nothing is yet known of the remote results.

11. DR. P. BRAY (Cardiff, introduced by Dr. A. G. Watkins): 'Sino-bronchitis: an Analysis of One Hundred Cases.' Out of 195 children with a chronic cough, 100 were found to have sinusitis associated with bronchopulmonary disease of varying severity. The cases were divided into two groups: asthmatic (44 per cent.) and non-asthmatic (56 per cent.).

Bilateral antral infection was the commonest kind of sinus infection. The associated chest conditions were: (a) bronchitic (44 cases: 10 asthmatic, 34 non-asthmatic); (b) lobular and segmental collapse (26 cases: 15 asthmatic, 11 non-asthmatic); (c) lobar collapse (30 cases: 19 asthmatic, 11 non-asthmatic).

There were fourteen cases of saccular bronchiectasis and twelve cases with slight cylindrical or irregular bronchial dilatation. Two of the latter were reversible.

The following conclusions were drawn:

(1) There is a kind of bronchitis, not obviously asthmatic, which is associated with sinus infection, and will clear up when the sinusitis is cured.

(2) The association of sinusitis and pulmonary collapse often follows pertussis; in this group neither the upper respiratory infection nor the chest condition is readily cured.

(3) In asthmatic children the combination of sinusitis and pulmonary collapse following pertussis leads in a large proportion of the cases to bronchiectasis.

12. MR. J. CROOKS (London): 'The Nature and Treatment of Sinusitis in Children.' In one year at the Hospital for Sick Children, Great Ormond Street, 340 children were found to have infected nasal sinuses. There is a close connexion between sinusitis and infection in the lower respiratory tract. The antra are more commonly infected than the other sinuses, and the onset is usually insidious from repeated upper respiratory infections. The changes in the sinus-lining membranes may be catarrhal, polypoid, or suppurative. The age of onset is often in the early school years, but the antra and ethmoids are present at birth, and they may be infected at any age. The symptoms are nasal discharge, nasal obstruction, cough. A child with catarrhal sinusitis may be cured by avoiding repeated infections (best attained by a holiday from school), and by the intranasal use of shrinking drops containing 'ephedrine' to promote drainage of the sinuses. He must be taught to blow his nose. More advanced antrum infection calls for lavage, which can be readily performed under local anaesthesia. Advanced disease of the lining membrane of the antra calls for its removal by radical operation, but this should not be undertaken unless persistent lavage fails to effect a cure.

Mr. Crooks showed a cinema film illustrating antral lavage with local anaesthesia in children.

12a. DR. J. LIND (Stockholm): At the Norrtull Hospital, Stockholm, in 1943 it was observed that out of 133 children ranging in age from 1½ to 15 years with presenting respiratory infections, 103 patients showed radiological sinus changes, mostly pronounced. Sinusitis is thus extremely common in respiratory infections and common also in children with banal coryza. We have used conservative treatment principally. We have had

favourable results with penicillin treatment. For the last year we have used penicillin-aerosol and employed a hood of transparent plexiglass with a bottom of soft plastic cloth which can be attached to most commercial penicillin sprays. The concentration of penicillin in the blood was satisfactory even after a short treatment (ten minutes), i.e. ¼-½ Oxford units an hour after inhalation.

As it has been possible to establish that the penicillin concentration becomes higher locally than with injection treatment, this form of therapy appears to us to be rational.

12b. DR. S. KRAEPELIN (Stockholm): At Norrtull's Hospital, Stockholm, during the period from October, 1947, to May, 1948, I began an investigation with Dr. Lind and Dr. Bjuggren with a view to throwing light upon the incidence, nature, duration, and social aspect of sinus affections in ordinary healthy children between the ages of three and six years who were looked after at home, and in those who were placed in day nurseries. Seventy-four children between the ages of three and six years were examined. Each child was examined at least three times at intervals of two months, irrespective of whether there were signs of infection of the upper air passages or not.

We observed that sinus affections were common even in so-called 'healthy' children in the ages of three and six years. About half of the children examined showed antrum change and positive antrum irrigation. No sure distinction can be made between the two categories of children concerning incidence. During a supplementary examination of 80 children (34 'home children' and 46 day-nursery children), chosen on the same principles, the incidence of antrum changes was verified.

Sinus affection is often present without the child otherwise showing any symptoms of infection of the upper air passages.

The changes in day-nursery children are notably more severe and protracted than in 'home children.'

There was good agreement between the puncture findings and the changes observed on the radiographs.

13. DR. B. VAHLQUIST (Stockholm): 'Serological Immunity in the Newborn Period.' Antibodies may be transferred to offspring via the placenta or in colostrum and milk. In human beings antibodies are easily transferred via the placenta. In many cases, e.g. for diphtheria, tetanus, whooping cough, antistreptolysin, antistaphylolysin, toxoplasma etc., the concentrations of the antibodies are much the same in the blood of the full term infant as in that of the mother. Correspondingly the γ-globulin concentration at birth is even higher in the child than in the mother.

Antibodies are secreted in human colostrum and to a less extent in milk. It has been a matter of dispute whether the child can utilize these antibodies or not. In order to elucidate this question the author administered orally human serum rich in diphtheria antibodies. In the first few days of life nine out of thirteen infants showed minute absorption, never exceeding 0·3 per cent. of the amount given and usually much lower than that. After the first week a faint trace of absorption could be demonstrated exceptionally. Similar experiments with antibodies of other types, e.g. against whooping cough, are in progress. They will be completed with trials using colostrum rich in antibodies obtained after vaccination during gestation.

DR. H. WALLER (London): 'Myoepithelial (Contractile) Cells surrounding the Secreting Alveoli of the Mammary Gland.' Dr. Waller showed slides of sections of the mammary gland of the goat, the work of K. C. Richardson, M.Sc., of University College, London, who has shown the existence of a network of myoepithelial cells, presumably contractile, surrounding the alveoli of the secreting gland. They exist in profusion along the ducts, where they are arranged longitudinally, and in the lacteal sinuses. The cells are distinct from the plain muscle of the gland and appear to furnish the means by which milk is expelled. Mr. Richardson's paper describing the cells and his method of staining them will be published by the Royal Society.

15. DR. R. B. MEYER (Birmingham, introduced by Dr. F. Braid): 'Salt Deficiency as a Cause of Vomiting in Infancy.' A baby who thrived only when taking large quantities of salt by mouth was described. Estimations of urinary sodium and chloride before and after the injection of desoxycorticosterone excluded adrenal hypofunction as a cause of this disorder and suggested that it was due to insensitivity of the renal tubules to the action of adrenal hormone in sodium reabsorption. It is possible that renal sodium leakage is more common than might be thought but that it has previously been missed because of superadded infection, of over-reliance on biochemical as opposed to therapeutic tests during the critical stage, and persistent use of small doses of DOCA instead of large amounts of salt on the assumption that marked salt depletion in infancy is due always to adrenal hypofunction. The lesion is probably an isolated one of the renal tubules and would fall into the same class as those in renal acidosis and renal glycosuria.

16. DR. D. J. CONWAY (London, introduced by Dr. B. Schlesinger): 'Nephrotic Crises.' In 1940, Farr and MacFadyen in New York described as nephrotic crises the acute febrile bouts, without demonstrable evidence of infection, which occur in nephrotic children and are accompanied by a sudden fall in the serum amino-acid level to 2·5 mg. or below.

At University College Hospital, London, the similarity of symptoms and signs in these crises has been confirmed. There is a rapid onset of abdominal pain and tenderness, usually without rigidity or inflammation of the abdominal wall, increased skin pallor and lassitude, rapid grunting respirations and pyrexia. Nausea and gaseous abdominal distension are common and a leucocytosis invariable. The condition clears rapidly after one to three days, even without chemotherapy.

Farr and MacFadyen consider that the crises are due to an acute disturbance of metabolism, because the characteristic fall in serum amino-nitrogen, as measured by the ninhydrin method, does not occur in pharyngitis or otitis media in these children. However, we have noted the same degree of fall in serum amino-acids in pneumococcal meningitis and peritonitis, the common skin erysipeloid which occurs in nephrotic children, and in a child who developed chicken pox. We feel that a similarity of clinical picture and fall in amino-acids does not exclude active infection.

REVIEW

Annali Italiani di Pediatria

We have received the first number of this new Italian paediatric journal (Vol. 1, Nos. 1-6, December, 1948), which is to be published bi-monthly at Cagliari, Sardinia. In his foreword the editor, Prof. Macciotta, points out that in spite of the large number of Italian paediatric publications there is still a long time lag between the submission of an article for publication and its appearance in print. This constitutes a serious obstacle to progress which he hopes the new journal will do something to eliminate.

The articles in this first number are followed by summaries in French and English, of which the former are more comprehensible to the Englishman than the latter. In welcoming this new addition to paediatric literature and extending to it our best wishes for the future, we hope that succeeding numbers will, for the benefit of those of us whose Italian is poor, contain more useful English summaries.